Cervical Pathology and Infection in Nomadic and Non-nomadic Women in Southern Iran

Thesis

Cervical Pathology and Infection in Nomadic and Non-nomadic women in Southern Iran

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Declaration

This thesis includes published work that has resulted from collaboration with Stephen W Duffy of the Medical Research Council Biostatistics Unit in Cambridge - UK, Ali Sadeghi- Hassanabadi of the Department of Community Medicine at Shiraz University of Medical Sciences- Iran, Zaleh Zolghadr of the Department of Obstetrics and Gynaecology at Shiraz University of Medical Sciences - Iran, Barat Oboodi and Farrokh Kaffashian of the Department of Bacteriology at Shiraz University of Medical Sciences - Iran, Farrokhshad Nili of the Department of Cytology at Shiraz University of Medical Sciences - Iran, and Alistair Williams of the Department of Cytology at University of Edinburgh – UK.

Chapters 3 and 4 contain three papers written by Stephen Duffy and myself.

All analysis and the writing of this thesis were performed by myself. None of the work contained in this thesis has been submitted for a degree of diploma or another qualification at any other University.

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To my family

Farrokh, Sara, Safa, and Sadra Kaffashian

Summary

Background: In 1990 , a study of the reproductive habits and cervical pathology in women of the Qashgha'i nomadic tribe, resulted in a high prevalence of cervicitis. This led us: to explore the likely infectious agents responsible for such a high prevalence; to assess the difference in cervicitis rates between nomadic and non-nomadic populations in the same area ; to determine the risk factors for and the relationship between cervicitis and bacterial vaginosis (BV) **Method and materials:** In 1996-1997 a study was carried out of 839 married women of the Qashgha'I tribe, 274 of the Lor nomadic tribe, and 388 non-nomadic urban women in southern Iran. A gynaecological examination, Pap smear and vaginal secretion for assessing cervicitis and BV by gram staining respectively were performed. Data were analysed by univariate and multiple logistic regression first with cervicitis as the outcome, then with BV as the outcome. Backward stepwise regression was used to assess multivariate effects on risk of cervicitis.

Results: Overall, the prevalence of cervicitis was 88% among Qashgha'I women, 85% in the Lor and 71% in the urban population. There was a significantly lower number of cervicitis cases in those over 40 years old ($p = 0.004$) and in those with a history of postpartum bleeding in Qashgha'i women. In the Lor tribe, the predictors were an increased risk after more than four pregnancies ($p < 0.01$) and the use of any contraception ($p < 0.002$). Among the urban population, the risk of cervicitis was increased with the use of oral contraceptive previously ($p = 0.03$) or currently ($p = 0.01$). BV was strongly associated with cervicitis, with a relatively high attributable risk.

Discusion: Both sexual and childbirth exposures may be associated with cervicitis in these populations. We found a very strong positive association between bacterial vaginosis and cervicitis. Bacterial vaginosis was a powerful risk factor for cervicitis even after adjustment for other risk factors for cervicitis. Attributable risks were also high, suggesting

that bacterial vaginosis may be implicated in 60% of cases of severe cervicitis cases. Both cervicitis and bacterial vaginosis are known to be associated with chlamydia. We found a strong positive association between high levels of histiocytes and presence of cervicitis (RR=8.69). Even taking account of the imprecision of this as an indicator of chlamydial infection, it is strongly suggestive of chlamydia as a major cause of this high rate of cervicitis.

Recommendation: In terms of the reproductive health status of the populations studied, the cervical inflammation is not only widespread, but also had a strong association with BV in all three populations. Abscence of dyskariosis, a high level of bacterial vaginosis, a strong association between cervical inflammation and BV, and a strong positive association between high level of histiocytes and the presence of cervicitis suggest that chlamydia is largely responsible for the cervicitis in the population. This should be verified by definitive testing and rectified by treatment programmes.

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Chapter 1

Introduction and Outline

This thesis reports on common cervical conditions and associated aetiology in nomadic populations in southern Iran, in particular among the women of the Qashqa'i nomadic tribe. The clinical and pathological background follow in chapter 2, but first it is necessary to introduce the populations studied.

1.1 Migratory Life in Iran

Migratory life in Iran has an ancient history. As recently as a century ago, thirty percent of Iran's total population was formed by migrant tribes. In the country's political field, their great influence and power has been instrumental in the rise and fall of government in the last few centuries. Migrant tribes have protected the territorial integrity of Iran and have played an important part in maintaining the country's independence. Animal husbandry combined with a nomadic way of life is the most important characteristic of the tribal community. However, it must be borne in mind that not all nomadic groups can be considered to be Tribes. Gypsies and urban animal husbandmen who move from one place to another do not fall within the category of Tribesmen.

Only groups of people having a social structure based on tribal hierarchical order, who have a distinct, delineated territory in which they move about and whose living is dependent on animal husbandry are called Tribespeople.

The sub-tribe is a political entity formed by clans and families who, according to familial ties and socio-political necessities, have kept together on common land. The tribes of Iran consist of about 96 sub-tribes. The clan is a socio-political unit consisting of a number of families. Clans are the most important class in this hierarchy. Some clans have no dependence upon any tribe. These are called independent clans. There are 547 independent clans, apart from those which are related to the tribal hierarchy. The family is the principal pillar of the clan. The hierarchy of migratory tribes after sub-tribe, clan and family include several smaller groupings, which can not be categorized or compared to one another without embarking on deep anthropological studies. Iranian tribes have about 180,233 families.

Although many Iranian groups consider themselves to belong to Tribes, according to the above definition only approximately 500,000 (7.7%) of the total populations of Iran actually live a migratory life. They manage about 24 million heads of livestock and are scattered in 20 of the 24 provinces of Iran, particularly on the slopes of Zagros Mountains (Figure 1.1). Whilst animal husbandry provides most of the tribal income, the art of handicraft has arisen as a complementary occupation, and has gradually found its way into their livelihood (*1,2*).

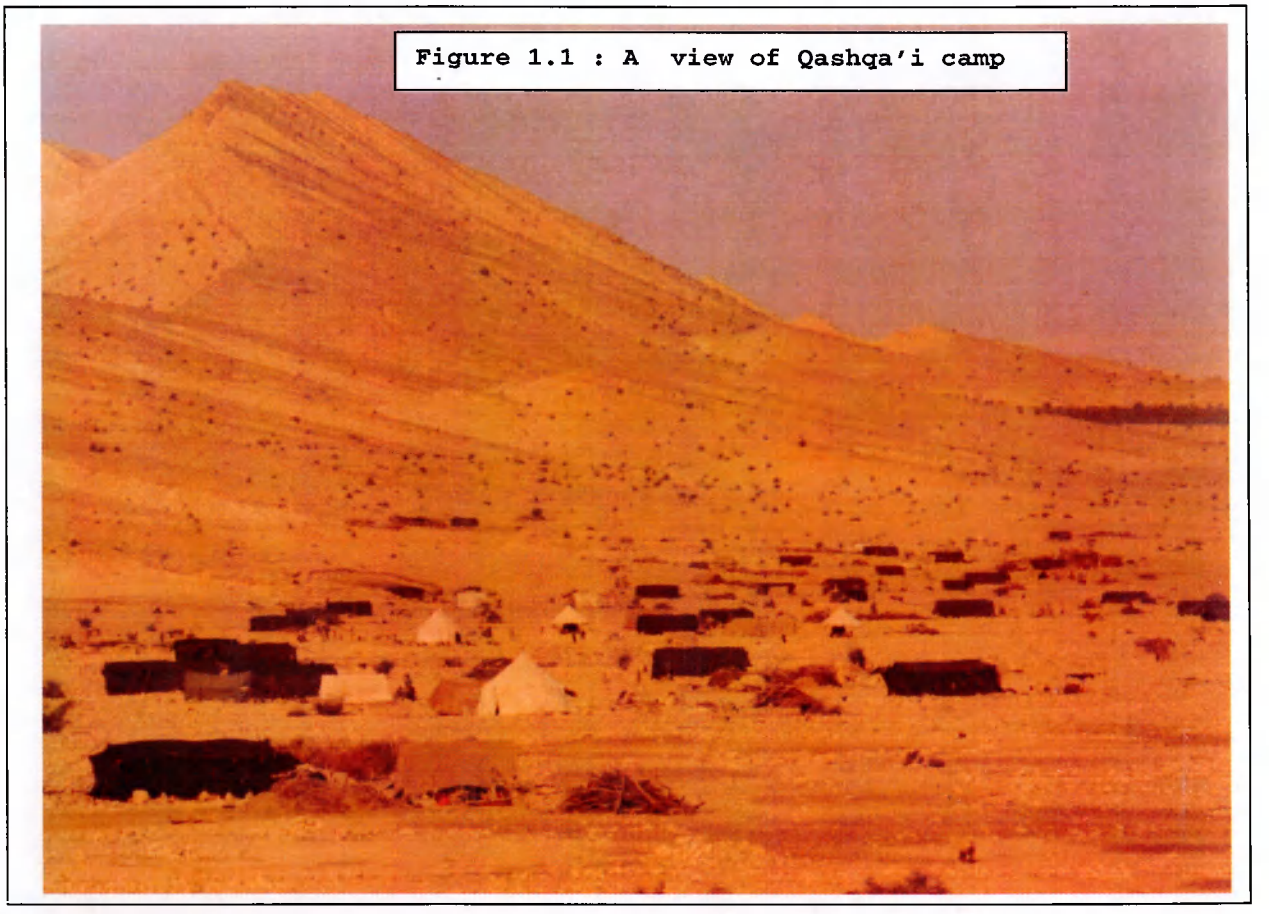

Figure 1.1 : A view of Qashqa'i camp

The tribes dealt with in this thesis are the Qashgha'i and Lur tribes of Fars province, Iran. Both are of the Muslim religion and have a broadly pastoralistic lifestyle.

1.2 Qashqa'i Nomads of Iran

Qashqa'i Nomads are the largest nomadic population in Iran. The origin of the Qashqa'is, like most present-day tribal confederation in Iran, is a conglomeration of clans of different ethnic origin: Luri, Kurdish, Arabic and Turkic. Most of the Qashqa'is are of Turkic origin, and almost all of them speak a western Ghuz Turkic dialect, which they call Turki.

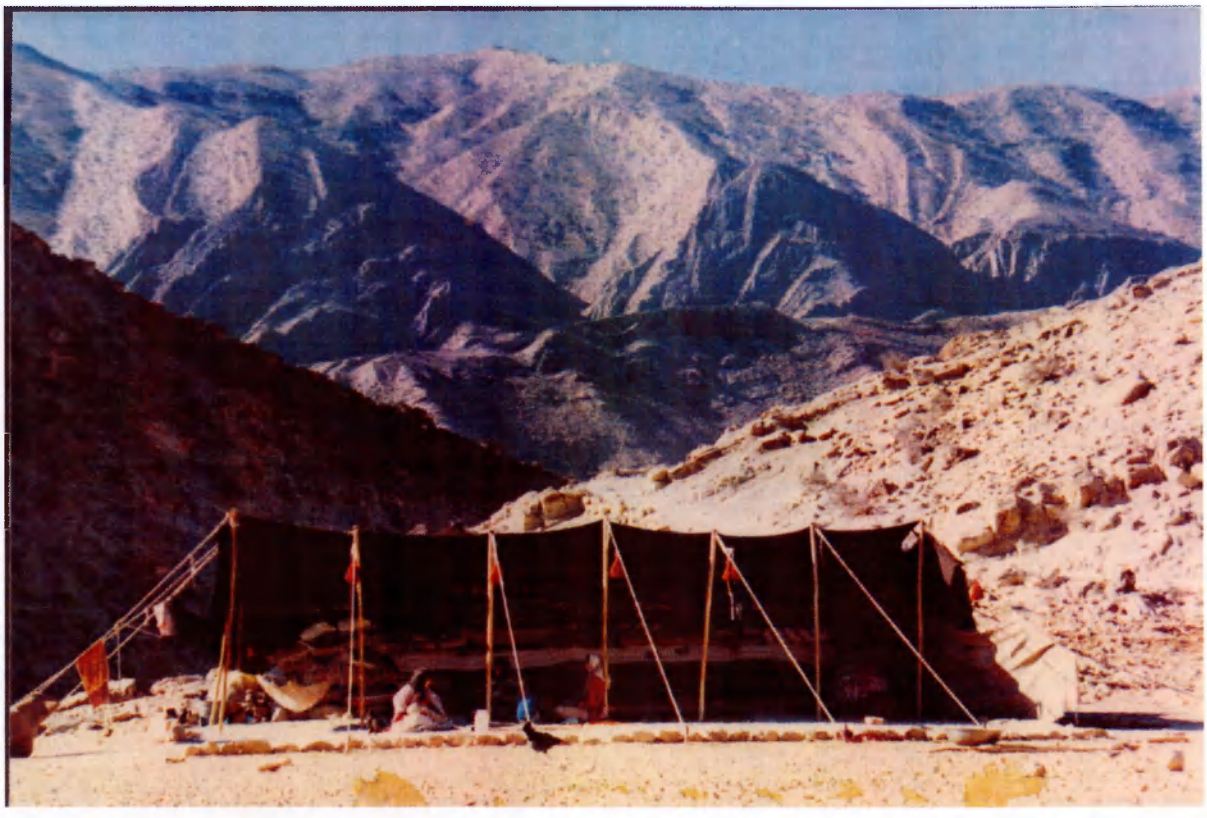

Figure 1.2: A view of a Qashqa'i tent in the Zagros Mountains

The Qashqa'is, in general, believe that their ancestors came to Persia from Turkestan in the vanguard of the armies of Hulagu Khan or Timur Leng. However, it seems more probable that they arrived during the great tribal migrations of the eleventh century. In all likelihood, they spent some time in northwestern Persia before coming to the province of Fars, in southern Iran. The Qashqa'is have stayed in Fars since the 11th century AD. In this region, Lush pastures are plentiful in the lowlands in winter and the uplands in summer (*3*).

1.2.1 The Qashqa'i Economy

The life of the Qashqa'is, like that of all pastoral peoples, is a perpetual search for grass. In winter, when the uplands are snowbound, they are to be found in the lowlands; in summer, when the lowlands are arid wastes, they move to the uplands. In the spring they invariably head north; in the autumn they have to move south. Thus their movements follow a regular, yearly pattern. Figure 1.2 shows a Qashqa'i camp.

The winter quarters of the Qashqa'is stretch all the way from Khuzestan to Larestan to the west, southwest, south and southeast of Shiraz. Their summer quarters are to the north and northwest of Shiraz. Their semi-annual migrations usually last from four to six weeks. During that time they may cover hundreds of miles. Some clans of the Qashqa'i tribe of "Amaleh", for instance, cover a distance of over 350 miles between their winter quarters, which are in the neighborhood of Afsar and Khonj, in southern Fars, and their summer quarters, which are within eighty miles of Esfahan (Figure 1.3).

Rights of transit, with few exceptions, are established by custom, Sometimes when the Nomads cross cultivated lands, there is friction between them and the settled population, for, unless they are strictly disciplined by their leaders, they may do considerable damage to the crops. On the other hand, the farmers can also profit from their passage. They trade with them, bartering their vegetables, wheat and barley for the tribesmen's dairy products; moreover, the sheep and goat manure fertilize their lands. Figure 1.4 shows a Qashgha'i migration.

Some of the pastures in the summer and winter quarters are owned by the tribesmen in common, but most belong to members of the chief's family. Qashqa'is play a major role in the economy of Fars province. They provide the villages and towns with animal hides, leather, meat, milk, butter, cheese, yogurt, charcoal and katira (gum tragacanth). They also sell rugs, carpets blankets, feedbags and horses (*3*).

Figure 1. Map of Iran. The major ethnic, tribal, and national-minority groups are indicated.

Figure 1.3: Map of Iran. The major ethnic, tribal, and national-minority groups are indicated

1.2.2 The Qashqa'i Tribes and Clans

Qashqa'i confederacy is divided into tribes (tavaef) and clans (tireha), and is made up of six major subtribes, the Amaleh, Darrehshuri, Farsimadan, Keshkuli, Shishboluki and Kashkuli Kuchek. The clan and family structures households and population estimates are given in Table 1.1 (*4*).

Table 1.1: The Qashqa'i Tribes and Clans

Tribe	Clans	Subclans (Bonko)	Households (families)	Individual (person)	Male	Female
Amaleh	47	203	4038	26727	13633	13094
Darrehshui	51	134	3345	23113	11721	11392
Farsimadan	24	69	2074	14169	7170	6999
Keshkuli Bozorg	46	111	2535	17174	8877	8297
Shishboluki	20	91	4210	26301	13171	13130
Keshkuli Kuchek	14	40	716	5033	26201	2413
Total	202	648	16918	114517	59192	55325

1.2.3 Qashqa'i Socioeconomic Organization

The Qashqa'i are historically socioeconomically stratified into (1) a small, wealthy ruling elite, (2) a large category of those having adequate access to the means of production (land, water, and animals), and (3) two small categories of those dependent on others for the means of subsistence.

Figure 1.4: Sheep and goat migrating with their owner

The vast majority of the Qashqa'i had always cultivated and pursued other nonpastoral subsistence activities in addition to pastoralism and therefore could rely on a range of economic strategies in case political events temporarily disrupted nomadic patterns(5).

1.2.4 Women's Status in the Qashqa'i Nomadic Tribe

The small nuclear or extended family household is the basic economic unit among the Qashqa'i, and all its members are of necessity drawn into the many tasks and responsibilities that sustain it: tending the different species of animals, preparing personal products, migrating, securing water and firewood, and so forth. The female is an integral member of the household in its division of labour during the different stages of her life cycle. Learning household tasks begins at a very young age (earlier than for the male). Her work is vital to the economic unit. The tent, woven by women out of black goat hair, is

small and is not structurally divided into female and male sections as is common with the tents of many other Middle Eastern nomadic peoples.

Women are responsible for milking, milk processing (yogurt, butter, cheese, oil, and so on), preparation of animal derivatives (skin, hair, wool), weaving, care of animals close to the tent, light firewood collection, bringing of water, gathering of wild plants, bread-baking, cooking, and child care. prepare the goods taken to town by men for trade (wool, oil, butter, dried curds, and skin),but women do not personally receive any payment. Men entrust the care of household supplies and town-acquired goods to women, who notify them when a particular product is in short supply.

Figure1.5: A Qashqa'i woman milking a goat

Qashqa'i women are weavers of fine carpets, blankets, and bags, all of which literally provide the substance of the home. They prepare the wool, card and spin it into yarn, collect natural substances for dyes, dye the yarn, prepare the loom, and weave. They plan the items to be woven, even their designs and colors, many years in advance, since major works can only be done once or twice a year, in the more sedentary periods of late winter (after the rains) and summer.

Figure1.6: A Qashqa'i woman weaving and spinning

Women and men share the process of making and breaking camp and migrating, without clear distinctions between "women's" and "men's" work. One major task is sex-linked, however: herd animals leave camp before daybreak, in the company of adolescent and adult males. Men in groups make decision concerning migration and choice of campsite. Women have little role in this process(*6*).

Marriage for the Qashqa'i is a vitally important aspect of the life. It is almost without exception that everyone marries. It is unusual for someone over twenty not to be married, or at least promised for marriage. Arranged unions are common, often as early as infancy (*7*). The women themselves have little say in the proceeding (*6*). Marriage tends to be within the clan, or even subclan.

The women of this tribe have a lifestyle characterized by hard physical work, as noted above (Figure 1.5 – 1.12).

Figure 1.7: A Qashqa'i woman drawing water from a well

Figure 1.8: A Qashqa'i woman carring a goat skin filled with water

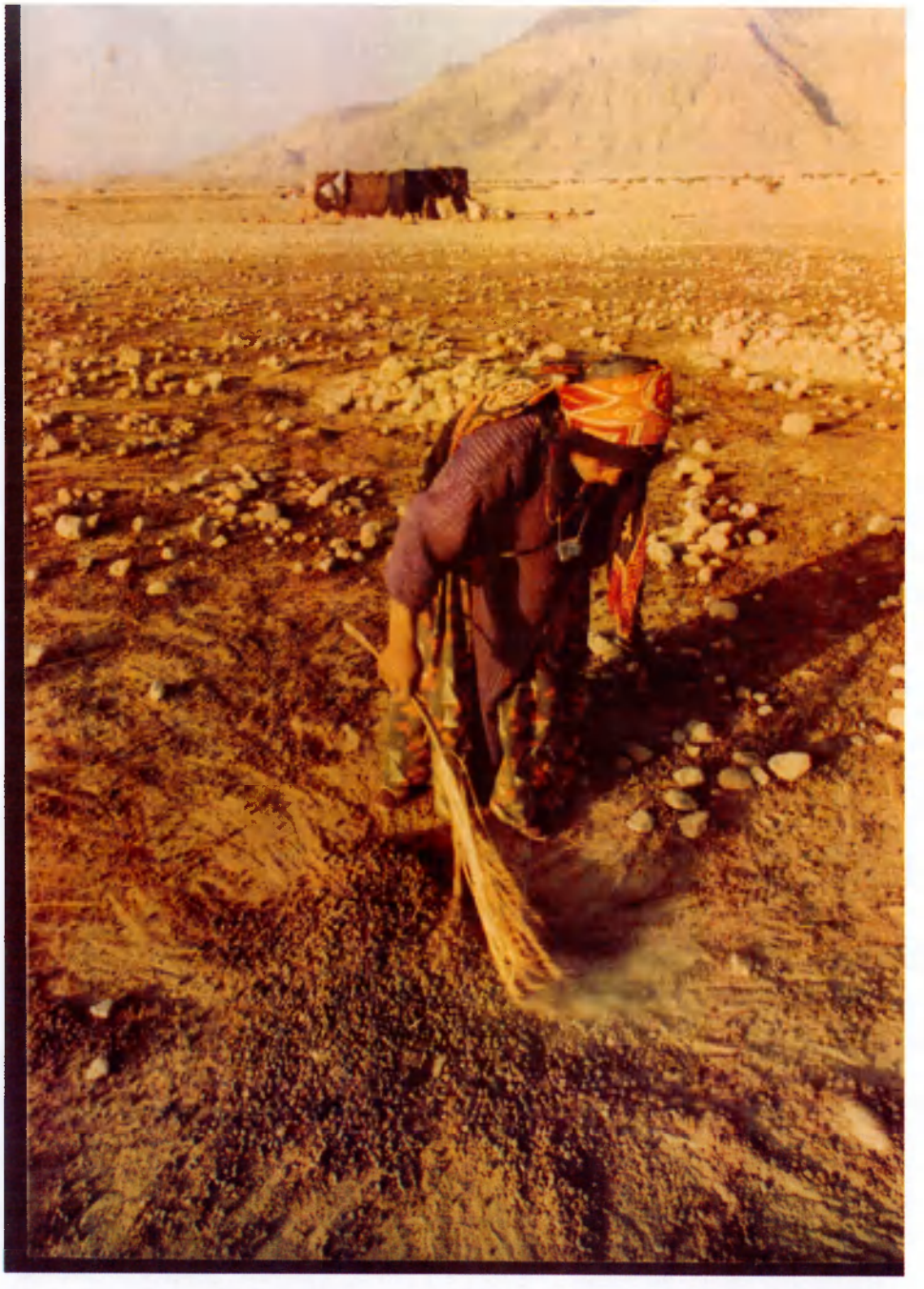

Figure 1.9: A Qashqa'i woman collecting sheep faeces for burning during winter

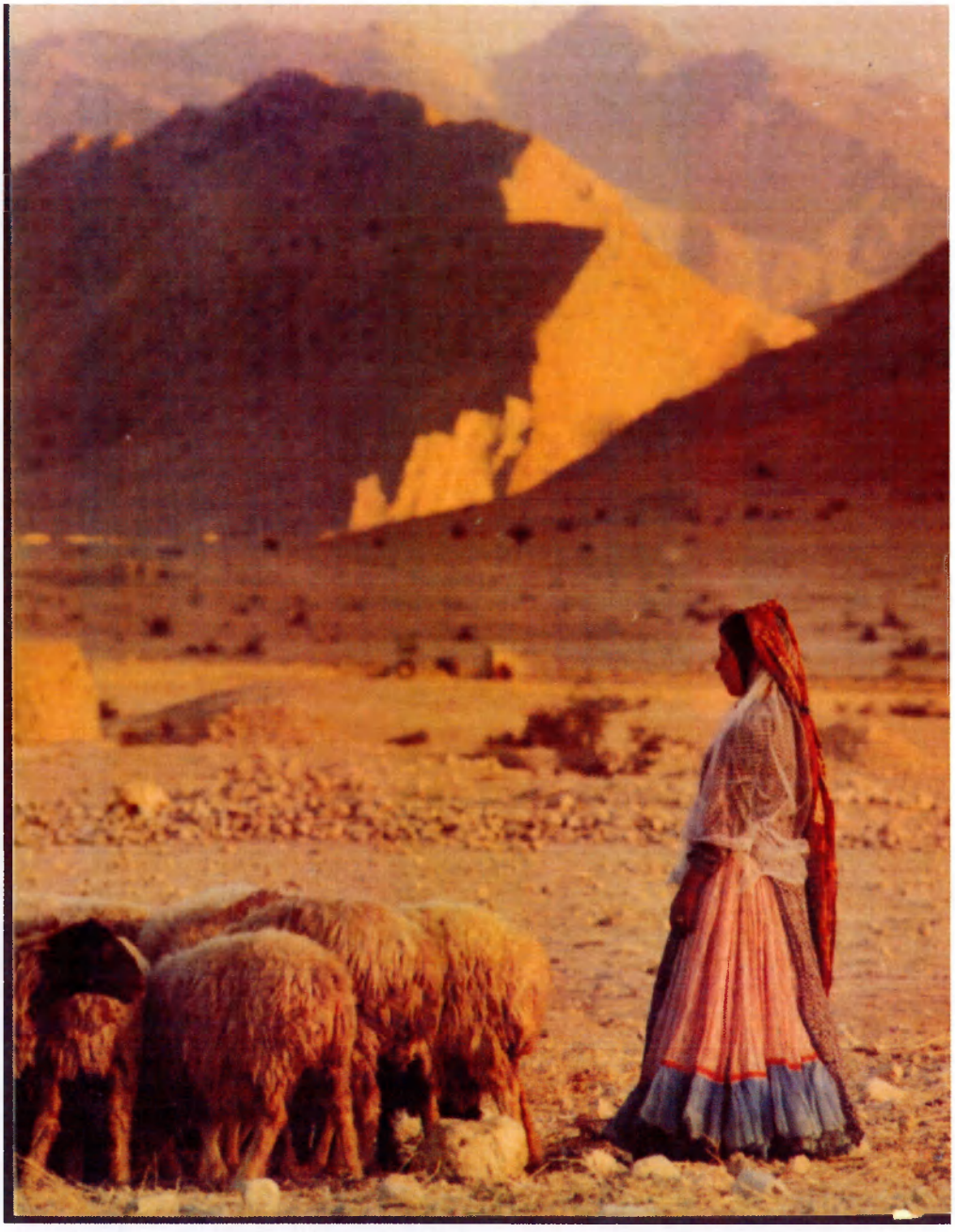

Figure 1.10: A Qashqa'i woman herding the sheep

Figure 1.11: A Qashqa'i woman carrying her child during migration or working

Figure 1.12 : A Qashqa'i woman pounding grain

1.3 Status of Women in the Mamassani (Lur) Nomads in Iran

Another major nomadic tribe in the region is the Lur or Lor of Mamassani. Mamassani township is located near the southern end of the Zagros Mountains. It is a district of Fars province about sixty miles northwest of Shiraz. The Mamassani Lurs mostly have settled in this fertile valley of Mamassani since 1576 AD. Some families used to live in tents in the summer, but in the winter permanently they live in the village house (Figure 1.13). Some families do not migrate and live in the village. They speak an Iranian dialect known as Luri. The Luri dialect is closer to Persian than is that of the Qashqa'i. The Lur engage in unspecialized herding and farming, a mixed form of subsistence. They have agricultural land and orchards. About half of the population own cattle. The Mamassani confederacy is divided into 4 tribes. The Mamassani's tribes and clans are shown in the table 1.2.

Table 1.2: The Mamassani Tribes and Clans

Tribe	Clans	Subclan (Bonko)	Households (families)	Individual (person)	Male	Female
Bakesh	10	37	593	3673	1886	1787
Javid	17	71	1842	10515	5373	5142
Doshmanziary	4	8	59	447	239	208
Rostam	12	54	862	5472	2828	2644
Total	43	170	3356	20107	10326	9781

The traditional role of women in the Lur tribe has been similar to that in the Qashgha'i in the past. Women tended to take the roles of dairy production textile work, while men make the decisions about herding and migration (figures 1.14-1.16). In addition, however, the Lur women fill an important role as herbalists and therapeutists.

In social and marital terms, the position of Lur women is similar to that of the Qashgha'i. One difference, at least according to anecdote, is that male polygamy is more common in the Lur tribe (Figure 1.13).

Figure 1.13: A view of the settled Lur population in Mamassani County

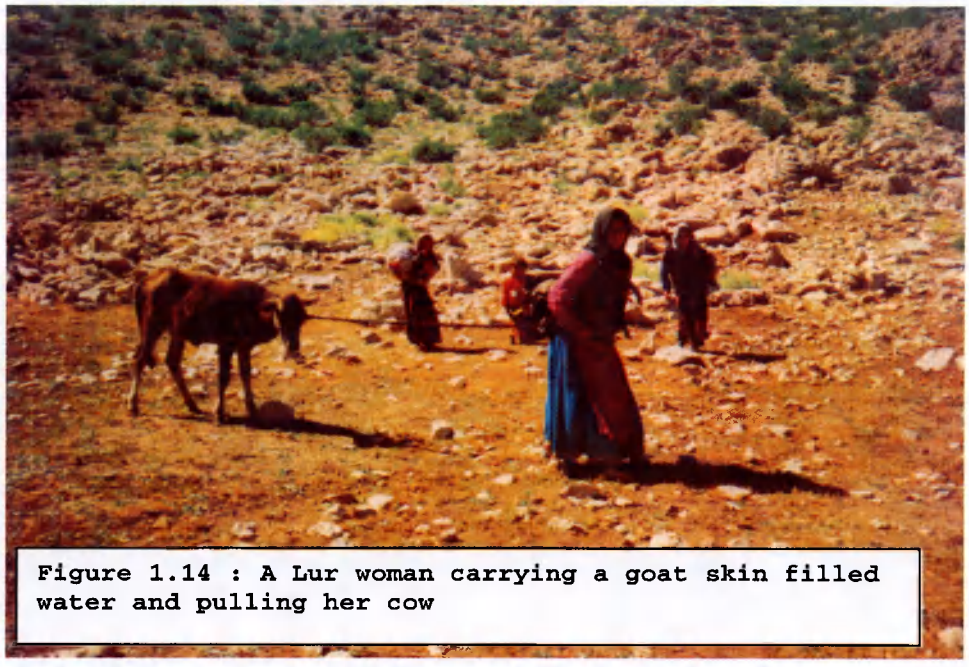

Figure 1.14 : A Lur woman carrying a goat skin filled water and pulling her cow

Figure 1.15: A Lur woman baking bread

Figure 1.16: A pregnant woman

1.4 The Status of the Nomads' Health in Iran

'Health for all by the year 2000' based on the Almata declaration of 1978 was the motto formulated by the World Health Organization (WHO). The main target for this drive, which aims at access for every individual to at least a village dispensary, will be the rural population in poor countries. Compared with urban populations, rural peoples everywhere are underserved in terms of health care, especially in developing countries. The nomadic peoples of the world are in need of special consideration.

Characteristics of nomads include scattered communities, and low average population density. These two criteria, added to their mobility, create specific problems regarding health and social services, and education.

When dealing with tribal people and especially with nomads, it is a matter of course to look at the 'total man in his total environment', and to consider all three components of the WHO definition of health: physical, mental, and social well-being. Our knowledge of nomads' health is limited because few epidemiological studies have been carried out specifically on nomadic groups(*8*).

The search for water is the main reason given by nomads for migration; the second most important reason is the need for grazing. Both, of course, go together, as water is a prerequisite for grazing. In essence, the animals migrate and the owners follow them.

The harsh way of life usually leads to a high tolerance of suffering in nomads. They are well adapted to the extreme climate. A considerable capacity for resisting flies and disease has also evolved.

Infant and child mortality, and accidental deaths associated with herding, tend to be high in nomadic communities. General health is comparatively good, thanks to satisfactory nutrition and existence close to nature, but some diseases, for instance trachoma, may occur frequently because of ecological and climatic factors.

Nomadic people are independent and self-sufficient in most fields. They have developed health services in which traditional healers and birth attendants are prominent. Certain treatments performed by highly trusted native doctors are undoubtedly beneficial. However the main therapeutic effects of traditional medicine are probably psychological. Where no

help from outside can be obtained and transport facilities are inefficient, traditional healers come into their own. Their practices undoubtedly have some value, but on occasions serious consequences arise, such as infection and septicemia(*9*).

Information on particular diseases is sparse but some surveys have been performed. As could be expected, zoonotic diseases are relatively common among pastoral nomads. Ultrasound examination, CCIEP and ELISA tests in order to study the prevalence of hydatid cysts of the liver were performed in survey of the Qashqa'i nomadic population in Iran. Hydatid cysts were detected in 1.2% by ultrasound, 13.7% by Elisa, 6.8% by CCIEP and 5.5% by both ELISA and CCIEP (*10*).

Brucellosis, causing abortion in cattle, has been responsible for great misery and economic loss in pastoral areas. The standard tube agglutination test (STAT), 2 mercapto ethanol (2ME) and Rose Bengal Test were used to assess the seroprevalence of antibodies to brucella in a survey among Qashqa'i nomads in Fars province. The seroprevalence of antibodies to brucella was demonstrated in 6 by STAT, 3.8 by 2ME and 7.8 by Rose Bengal(*11*).

The prevalence of positive antibody titer for H.Pylori and duodenal ulcer in Qashqa'i males, aged between 35-55 were 86.3 and 4.6 percent(*12*).

In a survey of reproductive habits and cervical pathology in women of the Qashqa'i nomads, a high prevalence (80%) of Cervicitis was observed (*13*).

1.5 Status of the Health System in Iran

Upon the official endorsement of Primary Health Care (PHC) as a major health care delivery strategy in the International Conference of Alma Ata in 1978, and later by the WHO, the government of Iran adopted this as the principal policy for delivery of health care throughout the country. The PHC network of Iran consists of a rural and an urban branch. The rural branch starts with a series of 'health houses' in the villages, each of which is responsible for 1500-1800 people. There is one male and one female 'Behvarz' or community health worker staff in each Health house. They are selected from the same area and often the same villages in which they will be working after their training. They receive two years of basic training in health topics and are mainly responsible for providing general preventive services, including immunization, family planning, advice on breastfeeding and nutrition, and environmental sanitation for all the individuals in their coverage area. They are also expected to provide basic therapeutic measures for minor illnesses and to refer other cases to their immediate Rural Health Center (RHC) for attention by a physician. Each RHC is responsible for four health houses or a population of 7,500 is staffed by one or two physicians and a number of paramedics, who are expected to closely monitor and support the activities of the health houses. The RHCs report to the District Health Center (DHC) for their administrative needs and should maintain close relationships with hospitals and other health institutions for their referrals. This latter activity is probably the weakest link in the system and needs specific attention. PHC network of the urban areas is still in the early stages of implementation. It aims to integrate the present therapy-oriented health centers into the public health-oriented PHC network. The smallest functioning unit in the urban branch of PHC network is the Urban Health Centre, which is similar to the RHC in staffing and the scope of services. Each Urban Health Centre covers almost 12,500 people and follows similar guidelines to the PHC in terms of services provided. However, more emphasis is given to health education,

nutrition, maternal and child health (MCH), and treatment of endemic diseases. The urban health centre is, like the RHC, under the administrative supervision of the DHC and maintains close relationships with hospitals for its referrals(*13*).

There is no special health centre for the nomads. If they are near the health house or when their summer or winter stations are in the village, they can use the primary health care network. The PHC network provides immunization services to the nomads, but its provision of other services is not as complete as to the non-nomadic population, due to the mobility of the nomads.

The nomadic community has been considered as a third community aside from the urban and rural ones, distinct from the latter due to its subsistence and cultural characteristics necessitating local mobility.

1.6 Motivation for Studying the Health Problems of the Nomadic Peoples

There are two basic motivations for research on the health problems of these populations. The first is to gain the information required to provide the most appropriate health care and public health services to these populations, within the limitations of the resources available. The second is to discover aspects of disease aetiology that may be apparent only in populations with lifestyles extremely different from those pertaining to populations in which most epidemiological research is carried out.

To take a very simple example, a large number of women in these populations have high parity, and associations of repeated childbirth with any given disorder would be more apparent in these women than in a population from northern Europe, for example, where there is generally low parity. It is the aim of this project to study cervical pathology in the

women of these tribes, with the ultimate objective of a better understanding of cervical pathology and infection in general.

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Chapter 2

Review

2.1 Women's Reproductive Health

Historically, the principal duty of women has been viewed as bearing children, and as serving as the foundation of families. The cost of women's health of discharging this duty has traditionally gone unrecognized. In many populations, notably in the developed countries, this situation no longer prevails, but it is certainly time for the nomadic populations to be considered here. Poor health, influenced by early and excessive childbearing, and premature death during labour or from weakness or exhaustion due to pregnancy and close birth spacing, were explained as destiny and divine will. Many women die or are chronically disabled from complications of pregnancy (*1*).

Health conditions in one phase of women's life affect not only subsequent phases, but also future generations. Research into women's health problems and analysis there of have shown that poverty has a disproportionate effect on women (*2*).

Other areas of concern include unequal access to and use of basic health resources, including primary health services for the prevention and treatment of childhood diseases, communicable diseases, malaria and other tropical diseases, and tuberculosis (*3*).

Women are also subject to particular health risks because of inadequate services to meet health needs related to sexually activity and reproduction. Reproductive tract infections (RTIs) are common diseases with profound social and health consequences, especially for women living in the Third Word. Yet, in allocating scarce human and financial health care

resources to developing countries, policy makers, program planners, and international donor agencies have generally given low priority to these reproductive diseases (*4*).

Cancers of all types are another major health threat to women. Cervical cancer is the most common form of cancer in women in most developing countries and overall is the second most common form of cancer in women. There are an estimated 450,000 new cases each year (a realistic figure that includes undiagnosed early cases would be high as 900,000), of whom 300,000 will die from the disease (*5*).

Reproductive health is an important aspect of general health. The latter has been defined by the World Health Organization (WHO) as "Physical, mental and social well being and not merely the absence of disease" (*6*). Reproductive health is the health and well being of individuals "in all matters relating to the reproductive system and to its functions and processes" (*7*).

Reproductive health promotion strategies should consider the needs of women at different times in their life-span and should give special attention to adolescents and women in their reproductive years as well as to gaps in existing service provision. Strategies adopted should ensure that women are involved in the planning and evaluation of these services. An approach to reproductive health that empowers women must be based on respect for women's autonomy and on the recognition that women will make appropriate decisions if they are given the necessary information and the means to do so.

Reproductive health care requires a wide range of information and services at the primary care level, and it also must provide referrals for services at other levels of the system. This range of provision includes family planning, safe delivery and postnatal care.

approximately 437,000 new cases of invasive cancer of the cervix diagnosed (about 12% of new cases of cancer in women) and in excess of 200,000 deaths from the disease. When males and females are considered together, cancer of the cervix is the fifth most common cancer worldwide, after cancers of the lung, stomach, breast and large bowel, accounting for an estimated 5.7% of all cases of the disease (*9*).

For each death from cancer of the cervix, it has been estimated that between 14 and 20 potential years of life before 70 years of age are lost. Assuming, therefore, an average of about 17 years of life lost per death, this gives an estimate of more than 3.4 million woman-years of life before 70 years of age lost due to cancer of the cervix each year worldwide.

The highest rates of cancer of the cervix, with corresponding relative frequencies of between 20% and 30%, occur in the developing areas of the world particularly parts of Asia, South America and Africa. Intermediate rates are evident in areas of eastern, northern and western Europe, while the lowest rates are seen in Australia and New Zealand, southern Europe, North America and western Asia (the Middle East) (*10*).

The concept that certain epithelial lesions are precursors of invasive squamous-cell carcinoma of the cervix has received significant support from a variety of epidemiologic and long-term follow-up studies. Several different methods have been used to study the natural history of different types of cervical cancer precursors (*11*).

Cervical intraepithelial neoplasia (CIN), a diagnosable premalignant lesion, has a peak incidence 10-12 years earlier than that of invasive cervical cancer. This type of lesion usually arises in epithelial cells undergoing metaplasia in the transitional zone of the

There is a lack of reliable information on many aspects of reproductive health, but the available data indicate that serious problems exist, particularly for women. An analysis by the World Bank and WHO showed that reproductive ill health accounts for more than 30% of the overall burden of disease and disability among women of reproductive age, compared to 12% for men (*8*).

Undertaking an approach to reproductive health that addresses the wide range of women's needs and provides relevant services offers opportunities for improving the effectiveness of delivery of health care. For example, a recent review identified lack of knowledge, fear of side effects and social and familial disapproval as the principal causes of unmet need for contraception in developing countries. Programs can be "successful if they reach beyond the conventional boundaries of service". It is already known that inclusion of diagnosis and treatment of RTIs in antenatal and family planning services would have beneficial effects (*8*).

Epidemiological studies can be used to indicate which women have limited access to care and are therefore at higher risk than others of maternal mortality. The universal risk factor is the fact of being female. Maternal sickness and death may be trigged by pregnancy, but frequently result from cultural, medical, and socioeconomic factors that devalue the status and health of women and girls (*1*).

2.2 Cervical Cancer and Cervical Cancer Screening

2.2.1 Epidemiology

Cancer of the cervix is the second most common cancer in women worldwide after cancer of the breast (excluding non-melanocytic skin cancers) and the most common in developing countries both in women and in both sexes together. Each year, there are

colposcopist, most often at the squamocolumnar junction of the cervix from cells in an aneuploid state. CIN is currently classified into three grades of severity-from CIN I (mild) to CIN III (severe). The changes in the affected epithelium occur along a spectrum ranging from minimal cytological changes to cells indistinguishable from malignant cells and extending the full thickness of the squamous epithelium (*11*).

2.2.2 Risk Factors

Large numbers of epidemiological studies have analysed risk factors for the development of cervical cancer and its precursors. Although the risk factors are similar for both cervical cancer and its precursors, the association with the risk factors is generally much stronger for cervical cancer than for precursor lesions. The major risk factors found in most studies are markers of sexual behavior, such as number of sexual partners, early age of first pregnancy and first intercourse, sexually transmitted diseases, and parity. In addition lower socioeconomic class, cigarette smoking, and immunosuppression from any cause have been observed to be associated with both cervical cancer and its precursors. Over the past 100 years, virtually every known sexually transmitted disease has been suggested as the aetiologic agent for cervical cancer precursors. The list includes Treponema pallidum, Trichomonas vaginalis, Candida Albicans, Chlamydia Trachomatis, and the herpes simplex viruses(HSV) (*11*). However, it is now established that the communicable agents primarily responsible are the oncogens types of the human popillomavirus (HPV).

2.2.3 Pathology of Preinvasive Lesions of the Cervix

At the time of menarche most young women have some endocervical-type columnar epithelium present on the portion (vaginal portion) of the cervix. This endocervical-type epithelium appears salmon red to the naked eye and has been referred to as erosion, ectropion, cervicalectopy, or native columnar epithelium. In response to a variety of stimuli, including low pH, trauma, hormonal factors, and cervico- vaginal infections,

shortly after menarche the columnar epithelium gradually becomes replaced by a stratified squamous epithelium. The replacement of columnar epithelium by a stratified squamous epithelium occurs by two different processes. One is called squamous metaplasia, and the other is the direct ingrowth of squamous epithelium from the periphery of the portio, referred to as epidermidization. As these processes occur, the histologic junction between stratified squamous epithelium and endocervical-type columnar epithelium moves inward toward the external cervical os. By age 40 years, the entire portio is covered by mature squamous epithelium in most women.

The transformation zone is defined as the region of the cervix that lies between the original squamocolumnar junction and the new or current squamocolumnar junction. The transformation zone is of critical importance in cervical pathology and colposcopy because it is the site at which CIN usually develops as well as the major locus for cervical carcinoma. Although CIN often extends into the endocervical canal, it rarely extends out onto the native squamous epithelium of the portio (*11*).

2.2.4 Cytology Screening for Cervical Cancer and its Precursors

Dr. George Papanicolaou first proposed cytology evaluation of cells obtained from the cervix and vagina in the 1940s as a method for detecting cervical cancer and its precursors. Since those early studies, cervical cytology has proved to be the most efficacious and cost-effective method for cancer screening (*11*). Appropriate management of early detection programs for cervical cancer is vital to efficiently reduce the burden of the disease. Early detection and screening have been successful in reducing mortality in some countries, but not in others, and this is most often due to poor management and implementation of inappropriate policies, screening mainly young women without sufficient coverage of older

women. Three-quarters of all women with cervical cancer are in developing countries, yet screening programs in these countries has had little or no effect.

For screening to be introduced, a basic health service infrastructure should exist in the region. This has to exist at both the primary health care level and at a district hospital level. At the primary health care level it is ideal if a mechanism exists to identify women in the target age group in the population served. However, the target group can be identified and screening brought to them in the absence of such a mechanism. It is not essential for a special service to be established for cervical cancer screening. The groups targeted for screening should be women at risk of cervical cancer as defined by risk factors including age and low socioeconomic status, as discussed above. The review of the demography of coverage by services may show that women at highest risk are not being adequately contacted by an appropriate service.

Mobile units or teams have been used in many circumstances for screening. If used in the context of an organized program, with the target population defined and personal invitations to individual women, mobile units can increase the coverage of scattered (rural) populations in the target age group. Mobile units that can provide diagnosis and simple therapeutic procedures for precancerous abnormalities are being evaluated in South Africa, in an effort to overcome the problem of women with abnormal smears failing to retained for management(*12*).

2.3 Community Observed Features In Cervical Cancer Screening

Papanicolaou devised a classification system for cervical cytology that divided exfoliated cells into five groups or classes:

- Class I smears were considered to be within normal limits.
- Class II smears were atypical (reactive) but not suggestive of malignancy.
- Class III smears had atypical cells suggestive but not diagnostic of malignancy.
- Class VI smears had atypical cells strongly suspicious for malignancy.

Because different cytology laboratories tended to interpret the class system differently and it was unclear how cytologic classes related to the histologic terminology used for cervical cancer precursors, the World Health Organization (WHO) established guidelines in 1973 for reporting cytologic diagnosis. The WHO terminology uses the terms dysplasia (which is CIN, subdivided into mild, moderate, and severe)and carcinoma in situ. It does not, however, allow direct cytohistologic correlation to be made, since the WHO terminology does not correlate with the SIL (CIN) histopathologic terminology (Table 2.1).

Table 2.1: Comparison of Papanicolaou, WHO, and Bethesda cervical cytology

Papanicolaou Class	WHO System	Bethesda System
Class I	Normal	Within normal limits
Class II	Atypical	Benign cellular changes (or) Atypical squamous cells of undetermined significance
Class III	Dysplasia	Squamous epithelial cell abnormality
	Mild dysplasia	Low-grade squamous intraepithelial lesion(SIL)
	Moderate dysplasia	High – grade SIL
	Severe dysplasia	High – grade SIL
Class IV	Carcinoma in situ	High – grade SIL
Class V	Invasive squamous cell carcinoma	Squamous-cell carcinoma
	Adenocarcinoma	Adenocarcinoma

In 1988, a National Institutes of Health consensus panel was formed to adopt a uniform terminology for reporting cervical cytology results. The classification system developed by this panel became known as the Bethesda System and became widely used in the United States. In 1991, a second consensus panel was convened to evaluate the strengths and

weaknesses of the Bethesda System classification in clinical practice. In the basis of this re-evaluation, the Bethesda System was modified in 1991 (Table 2.2).

Table 2.2: The 1991 Bethesda System

Adequacy of the specimen
Satisfactory for evaluation
Satisfactory for evaluation but limited by....(specify reason
Unsatisfactory for evaluation.. (specify reason)
General categorization (optional)
Within normal limits
Benign cellular changes (see descriptive diagnosis)
Epithelial cell abnormality (see descriptive diagnosis)
Descriptive diagnosis
Benign cellular changes
• Infection
Trichomonas vaginalis
Fungal organisms morphologically consistent with Candida sp
Predominance of coccobacilli consistent with Actinomyces sp
Cellular changes associate with herpes simplex virus
Others
• Reactive changes
• Reactive cellular changes associated with:
Inflammatory (includes typical repair)
Atrophy with inflammation ("atrophic vaginitis")
Radiation
Intrauterine contraceptive device (IUD)
Other
• Epithelial-cell abnormalities
Squamous cell
Atypical squamous-cells of undetermined significance:(quality)
Low-grade squamous intraepithelial lesion (SIL) encompassing HPV mild dysplasia/cervical intraepithelial neoplasia (CIN)1
High grade SIL encompassing moderate and severe dysplasia, carcinoma-in-situ (CIN)/CIN2, and CIN3
Squamous-cell carcinoma
• Glanular cell
Endometrial cells, cytologically benign, in a postmenopausal women
Atypical glanular cell of undetermined significance: (qualify)
Endocervical adenocarcinoma
Endometrial adenocarcinoma
Extrauterine adenocarcinoma
Adenocarcinoma, not otherwise specified
Other malignant neoplasia: (specify)
• Hormonal evaluation (applies to vaginal smears only)
Hormonal pattern compatible with age and history:
Hormonal pattern incompatible with age and history: (specify)
Hormonal evaluation not possible

Like any classification system, the Bethesda System has both strengths and weaknesses. Its major features are that it requires (a) an estimate of the adequacy of the specimen for diagnostic evaluation: (b) a general categorization of the specimen as either

being within normal limits, showing benign cellular changes related to inflammation, or showing an epithelial abnormality: and (c) a descriptive diagnosis that includes evidence of infection, inflammation, reactive changes, and a description of epithelial cell abnormalities. This system provides clear criteria for determining whether a specimen is adequate for evaluation. In addition, the terminology closely correlates with histopathologic terminology; the terms low-grade and high-grade squamous intraepithelial lesion are used to designate cytologic changes that correlate with low- and high-grade SIL (CIN 2,3), CIN, or CAIN lesions. Direct cytohistologic correlation can be made, a fact that is an important feature for quality control in cytology laboratories. In addition, the Bethesda System attempts to separate epithelial changes secondary to inflammation or repair from those associated with cervical cancer precursors, whenever possible. One potential drawback of this classification is that it allows cytologic changes suggestive of HPV infection to be classified together with low-grade squamous epithelial lesions. Although based on sound scientific and pathologic evidence, this grouping increases the possibility for overdiagnosis of low-grade squamous intra-epithelial lesions because the cytologic changes consistent with HPV infection are often mimicked by other conditions, such as infections with Trichomonas or Candida organisms (*11*).

2.3.1 Squamous Metaplasia

Metaplasia means production of one type of adult tissue by cells, which normally differentiate to another type of tissue. Chronic inflammation and persistent stimulation are the main causes. Metaplasia involves the epithelium of endocervical glands as well as the surface epithelium. Squamous metaplasia is frequently accompanied by chronic cervicitis, which makes the cellular border hazier and produces vesicular vacuolation or perinuclear halo of the cytoplasm (*13*).

2.3.2 Inflammatory Cell Changes

Inflammation may play a causative role in exfoliation of various abnormal cells. Insufficient maturation of the stratified squamous epithelium in prepubertal and postmenopausal periods or in deficiency of estrogen may be susceptible to bacterial infection. Inflammatory changes may be caused by many bacteria, such as streptococci, staphylococci, gonococci and Neissera Catarrhalis. Histologically the mucosa is oedematous and erosion may occurs productive inflammation, in which proliferation of epithelial cells occasionally occurs, is more important than acute inflammation from the standpoint of cytodiagnosis. The cytology is described by Takahashi (*13*) as follow:

1) Acute and subacute inflammation: The smear is smudgy in appearance because of the preponderance of neutrophilic leukocytes, degenerative or necrotic cells, cellular debris, and causative microorganisms or protozoa.
2) Chronic inflammation: There are no peculiar cytologic features of chronic inflammation. Nuclear hypertrophy, hyperchromatism, remarkable Karyosomes and occasional multinucleation that may mimic malignancy is often seen B12 deficiency produce a similar appearance cytology. Folate deficiency causes impaired DNA synthesis, which is reflected in the cell nucleus. It has been reported that about one fifth of women taking oral contraceptives showed similar cytologic changes to those with folate or vitamin B12 deficiency because of impairment of folate metabolism, although less severely involved quantitatively (*13*).

2.3.3 Cervicitis

Cervicitis was once called the "ignored counterpart in women of urethritis in men" (*14*). A number of studies have focused on cervicitis since then, and available information has helped in understanding the importance of the cervix as a reservoir for sexually transmitted infections. Cervical infections may spread to the upper genital tract, the foetus, or to a

sexual partner. It is therefore important that clinicians performing gynaecologic examinations be sensitive to signs of cervicitis and liberal with cervical culturing, as well as for them to adequately treat all infections (*15*).

2.3.3.1 Definition

The nomenclature used for cervicitis has been confusing. Terms such as "cervical erosion," "cervical ectopy," "papillary cervicitis," "follicular cervicitis," "hypertrophic cervicitis," and "chronic cervicitis" have been used for clinical, colposcopic, or histopathologic evidence of cervicitis, often without evidence for a correlation with infection. Recently it has been recognized that cervical "erosion" or "ectopy" are caused by extension of the endocervical columnar epithelium to the ectocervix, a frequent but normal finding among younger women. Histopathologic evidence of "chronic cervicitis" is present in almost every cervical biopsy and apparently has no pathologic significance.

A cervical infection can involve the endocervix (mucopurulent). Simple criteria for the clinical diagnosis of mucopulent cervicitis have recently been developed (*14*).
The inflammation is characterized by the presence of polymorphonuclear leukocytes (PMNs) in the cervical mucus (mucopus). In some cases the yellow color of mucopus can be appreciated directly during a pelvic examination or by contrast to the white cotton on a swab that has been rotated in the cervical canal. In other cases, microscopic examination of gram-stained cervical mucus is needed to reveal the presence of PMNs (*15*).

2.3.3.2 Significance

Cervicitis as such is probably not harmful. Its significance resides in its association with pathogens such as Neisseria gonorrhea, Chlamydia trachomatis, Trichomonas vaginalis, and HSV. From the cervix, N. gonorrhea and C. trachomatis can spread to the upper genital

tract. These infections can also be transmitted to sexual partners and cause urethritis, epididymitis, or prostatitis. It has been estimated that about 10% of women with untreated C trachomatis or N. gonorrhea infections of the cervix will develop pelvic inflammatory disease (*16*). The spread of infection from the cervix to the upper genital tract before or after termination of a pregnancy can cause amnionitis, premature rupture of membranes, chorioamnionitis, premature delivery, and postpartum or postabortion endometritis (*17*). The causative microorganisms can also spread to the unborn baby during delivery, causing conjunctivitis (N. gonorrhea, C. trachomatis), Pharyngitis (C. trachomatis), pneumonitis (C. trachomatis), or encephalitis (HSV). Thus, the early recognition and adequate treatment of cervicitis is tremendously important in the prevention of ascending infections and transmission of pathogens to sexual partners and the foetus (*15*).

2.3.3.3 Diagnosis of cervicitis

Signs that may suggest cervicitis are easily induced bleeding (friability), erythema, and oedema or cervical ectopy (*18*). Friability may be noted when a speculum touches the ectocervix or when the cervical canal is swabbed.

A number of diagnostic procedures help to confirm the diagnosis of mucopurulent cervicitis, including the "swab test", gram staining of and microscopic examination of a cervical mucus specimen, colposcopy, cytology, biopsy, and cultures or antigen-detection tests for specific pathogens. Visual inspection of cervical mucus and the swab test are screening methods that can be performed by anyone involved in the pelvic examination of women. Purulent cervical mucus indicates a high concentration of PMNs in the mucus, and in some cases of mucopurulent cervicitis, mucopus may be a quite obvious finding, while in other cases the yellow colour of cervical mucus may be revealed when contrasted against the white color of a cotton-tipped applicator. In some infected women, cervical mucus may

be colourless when inspected with the naked eye, but an increased content of PMNs may be revealed when a mucus smear is gram stained and examined under a light microscope. There is no unanimity among clinicians about minimum number of PMNs that must be present in a gram-stained cervical specimen in order to make the diagnosis of mucopurulent cervicitis. Brunham and associates isolated C. trachomatis from 85% of women with 10 or more PMNs per 1,000 x field, as compared with 20% of women with fewer than 10 cells per field ($p < 0.01$) (*14*). Willmot also studied women visiting an STD clinic, confirming the association between C. trachomatis infection and 10 or more PMNs per oil immersion field (*19*). Furthermore, among women whose cervical gram-stain specimens had 10 or more PMNs per microscopic field, those with a purulent cervical discharge had a higher infection rate with C. trachomatis (38%) than those with opaque mucus (18%) (*19*). Moscicki and co-workers suggested using a cut-off point of 5 or more PMNs per high-power field in gram-stained cervical specimens. In their study, the sensitivity of cervical gram staining for chlamydial infection was reduced from 91 to 38%, and the specificity was increased from 65% to 89%, when the threshold value for cervical gram stains was changed from 5 or more to 15 or more PMNs (*20*). Table 2.3 shows sensitivity, specificity and predictive vales for various cut-off points of numbers of PMN's observed as a diagnostic indicator of chlamydial or gonococcal infection (15). As we would expect, the higher the stipulated cut-off, the lower the sensitivity and the higher the specificity, both ranging from very low to very high values.

Table 2.3 : Diagnosis value for chlamydial or gonococcal infection of different cutoff points for the numbers polymorphonuclear leukocytes per 1,000 x microscopy field in gram-stained cervical specimens

	Numbers of PMNs used as cutoff point				
	>10	>20	>30	>40	>50
Sensitivity	80%	65%	47%	29%	11%
Specificity	48%	67%	80%	90%	97%
Positive PV	33%	39%	43%	48%	53%
Negative PV	89%	86%	82%	80%	87%

Thus, there is no natural cutoff point for the number of PMNs in gram-stained cervical specimens. However, if one wants to base treatment decisions or decisions about whether or not cervical culture specimens should be obtained on the results of cervical gram stained, it seems that 30 or more PMNs per 1,000 x field is a reasonable cutoff point(*15*) Inflammatory changes are usually seen in a Papanicolaou smear from patient with cervicitis. In a recent study, infection with C. trachomatis and T. vaginalis, but not N. gonorrhea, was associated with inflammatory changes in cytology smears. Chlamydia trachomatis infection was associated with the presence of reactive or atypical metaplastic cells, transformed lymphocytes, histiocytes, plasma cells, and PMNs in the smear. Large, distinct, inclusion-containing vacuoles in epithelial cells were significantly associated with C. trachomatis, but the positive value of this finding for C. trachomatis infection was only 22%. The presence of transformed lymphocytes and or 30 or more histiocytes per 400 x field had the highest positive predictive value for C. trachomatis infection (50%) (*21*). Metaplastic cells punctuated by microvacuolea with small central eosinophilic granules had a much higher positive predictive value for C. trachomatis infection (92%), but the sensitivity of this finding was still low (63%) (*22*). Thus, cytology cannot replace the clinical and bacteriologic identification of mucopurulent cervicitis or C. trachomatis infection, but women with evidence of chlamydial infection on a routine Pap smear should be re-evaluated with a chlamydial culture (*15*).

2.4 Common Infections in the Reproductive Tract

2.4.1 Clinical Microbiology of the Female Genital Tract

The microbiology of the female genital tract is indeed complex. In healthy women, the vagina contains a bacterial colony forming 109 units/gram of secretions. Isolates found commonly in the lower genital tract include a variety of aerobic and anaerobic bacteria, yeast, viruses, and parasites (Table 2.3). Influences upon these include the phase of the menstrual cycle, sexual activity, contraceptive use, childbirth, surgery, and antibiotic therapy. The upper genital tract is usually sterile, but bacteria from the lower genital tract may ascend into the uterine cavity, fallopian tubes, or pelvic peritoneum because of menstruation, instrumentation, foreign bodies, or surgery or other predisposing factors.

Table 2.4: Classification of Microorganisms commonly found in the female genital tract

Bacteria	**Viruses**
Aerobic and facultative bacteria	Cytomegalovirus
Gram-positive cocci	Herpes simplex virus
Staphylococcus aureus	Human papiloma virus (HPV)
Staphylococcus epidermidis	Human immunodeficiency virus(HIV)
Staphylococcus saprophylicus	Hepatitis B virus
Enterococcus Faecalis(group entrococcus)	**Anaerobic bacteria**
Enterococcus Faecium(group D enterococcus)	Gram-positive cocci
Streptococcus agalactiae(groupBstreptococcus)	Peptostreptococcus
Streptococcus bovis (group D nonenterococcus)	Peptostreptococcus anaerobius
Streptococcus canis(group G streptococcus)	Peptostreptococcus asaccharolyticus
Streptococcus pneumonia(Diplococcuspneumonia)	Peptostreptococcus Magnus
Streptococcus pyogenes (group Astreptococcus)	Peptostreptococcus Prevotii
Viridous group streptococci	Gram-positive bacilli
Gram-positive bacilli	Actinomyces species
Corynebacterum species	Blfidobacterium species
Gardnerella	Eubacterium species
Dephtheroid	Lactobacillus species
Lactobacillus species	Propionibacterium species
Listeria monocytogenes	Clostridium species
Gram-negative cocci	Gram-negative cocci
Neisseria gonorrhea	Veillonellaceae
Gram-negative bacilli	Gram-negative bacilli
Citrobacter species	Bacteroides (Bacteroides fragilis group)
Enterobacter species	Bacteroides species, other
Escherichia coli	Bacteroides capillosus
Klebsiella Pneumonia	Fusobacterium species
Morganella morganii	Porphyromonas
Proteus mirabilis	Porphyromonas asaccharolytica
Acinetobacter species	Prevotella
Pseudomonas aeruginos	Prevotella bivia
Gardnerella vaginalis	Prevotella disiens
Mycoplasma	Prevotella
Mycoplasma Hominis	Prevotella bivia
Ureaplasma urealyticum	Prevotella disiens
Mycoplasma genitalium	Prevotella melaninogenica
Intracellular bacteria	Formerly T form
Chlamydia trachomatis	**Yeast**
	Candida albicans
	Candida Kefyr
	Parasites
	Trichomonas vaginalis

2.4.1.1 Yeast

Yeasts are commonly isolated from the vagina. *Candida albicans* is clearly the most common yeast found in vaginal cultures, but other *Candida* are seen in 10-15%. In vaginitis, yeasts are commonly identified by direct microscopy, but culture is helpful in problem cases (*23*). Vaginal candidiasis is treated topically by a number of agents or by new oral agents. Although the initial cure rate for vaginal candidiasis is good (80-90%), recurrent infection is a problem (*24*).

2.4.1.2 Trichomonads

Trichomonads vaginalis, a flagellated parasite, is found in vaginal secretions of approximately 6% of women and is responsible for up to one-quarter of cases of infectious vaginitis. *T. vaginalis* is commonly detected by direct microscopy of a wet mount of vaginal secretions. These flagellates are larger than white cells and have great motility in fresh preparations.

T vaginalis may also be detected on the Papanicolaou smear, but the reliability of this technique is uncertain (*25,26*). Trichomoniasis is treated with metronidazole (Flagyl) or related 5-nitroimidazole derivatives. Because this organism is transmitted sexually, partners should be treated as well. In the last few years, relative resistance to metronidazole has become common. Most cases do respond, however, to a higher dose of metronidazole (*27*).

2.4.1.3 Chlamydia Trachomatis

Chlamydia are intracellular bacteria that are involved in a variety of genital and prenatal infections (*28*). From 2 to 25% of women have positive cervical cultures for C. trachomatis . Isolation rates of approximately 25% are found in high-risk groups, such as women attending sexually transmitted disease clinics. In males, Chlamydia are responsible for many instances of nongonococcal urethritis, and in females, evidence of their virulence has

been accumulating. Chlamydia is though to be a major cause of inflammation (*21*). Tetracyclines are the antibiotics of choice in treating chlamydial infection. High doses of ampicllin or amoxicillin also appear to provide some cures.

2.4.1.4 Viruses

Several viruses are commonly found in the female genital tract. Herpes simplex virus is a well-known cause of an ulcerative, usually self-limiting, lower genital tract infection. Herpes can also be asymptomatic. In surveys of adult females, this virus has been isolated from the genitalia in 0.02-1%. Serologic surveys show that 35% of reproductive age females have serum antibody to herpesvirus, type 2. The most reliable method for detecting herpes infection is the culture. Clinical diagnosis and Papanicolaou smears are less sensitive. Acyclover is available for treatment or prevention of genital herpes infections.

Human papiloma virus (HPV) is the causative agent of genital warts, condylomata accuminata. The marked rise in interest in this virus recently stems from its dramatic increase in frequency and its relationship to genital tract malignancy (*29*). The common HPV types are 6, 11, 16, and 18 (*30*). The first two are more common and are usually associated with benign genital warts, whereas the latter two are more likely to be associated with higher grades of cervical intraepithelial neoplasia or invasive carcinoma (*24*).

2.4.2 Bacterial Vaginosis

Bacterial Vaginosis (BV) is the most prevalent cause of complaints of vaginal discharge in women of reproductive age. It is characterized by a copious, malodorous, nonirritating vaginal discharge. BV is now recognized as a very common entity. Although lack of standardized diagnostic criteria has limited epidemiological studies, it has been estimated that BV occurs in perhaps 15% of private gynecology patients, 10-30% of pregnant women, and 2-25% of college students (*31,32*). In STD clinics, the prevalence has ranged

from 12 to 61%. Between one-third and three-fourths of women with BV have no attributable symptoms. Table 2.5 summarizes the characteristics of BV and normal vaginal secretions. The diagnosis of BV should be based upon the general characteristics of volume. Colour, adherence, and viscosity and upon specific features of high pH, ``amine" odor with KOH (Potassium hydroxide), homogeneous consistency, and presence of clue cells. True clue cells are epithelial cells that are so heavily stippled with bacteria that the borders are obscured. Epithelial cells with few bacteria and clear borders should not be identified as clue cells.

Table 2.5: Characteristics of normal secretions and vaginitis

Feature	Normal	Vaginosis	Trichomonas	Yeast
Appearance	White, follicular High viscosity		Gray, yellow, or white: Frothy or milky / creamy	
pH	<4.5	>4.5	>4.5	<4.5
Clue cell	Absent	Present	Absent	Absent
Trichomonas	Absent	Absent	Present	Absent
Mycelia	Absent	Absent	Absent	Present

Gram staining of vaginal secretion may also be used to diagnosis BV. Specimens from patients with BV have numerous mixed bacteria and a paucity of lactobacilli. Clue cells may be seen clearly. In comparison, patients with normal secretions have fewer bacteria, which are predominantly lactobacilli cell types. There are a considerable number of patients with an intermediate type of flora on Gram stain. These may be developing BV or perhaps resolving it spontaneously. The three bacterial morphotypes that were most reliable in establishing a diagnosis of BV were lactobacilli seen as large Gram-positive rods, Gardnerella and Bacteroides seen as small Gram negative or Gram-variable rods, and Mobiluncus seen as curved Gram-negative or Gram-variable rods.

These morphotypes have been used to establish a 10-point BV score in which 0-3 is normal, 4-6 is intermediate, and 7-10 is BV. This scoring system has acceptable interobserver variability after some training and experience of the slide reader (*33*).

The Gram-stained smears have good-to-excellent sensitivity (62-100%) and a good-to-excellent positive predictive value (*24*). The treatment of bacterial vaginosis is directed toward re-establishing the normal balance of bacteria in the vagina. Metronidazole, taken orally twice daily for several days, is the initial recommended treatment (*34*).

2.5 Definition of cervicitis in this thesis

Much of the work described in the following chapters relates to cervicitis. We categorise cervicitis into four classes: no cervicitis, mild, moderate and severe cervicitis. The categories are defined on the basis of inflammation, as in Kiviat et al (21). This in turn is measured by the quantity of polymorphonuclear leukocytes (PMNL's) on cervical smears. The classes are:

No cervicitis: no PMNL's seen.

Mild cervicitis: PMNL's in less that 25% of microscope fields.

Moderate cervicitis: PMNL's in 25-75% of microscope fields.

Severe cervicitis: PMNL's seen in more than 75% of microscope fields.

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Chapter 3

A survey of cervical cytological observations in Qashqa'i women: Prevalence and predictor of cervicitis

3.1 Material and Methods

3.1.1 Subject and Data Collection

Between 1991 and 1992, a survey of 1015 married women members of the Qashqa'i tribe was carried out. The women were selected by a stratified random sample, in two tiers to give 1000 women in proportions representative of the six tribes of the Qashqa'i , and of clans within the tribes. The samples units were the subclans (Bonko) within the clans (Table 1.1).

The Bonko were selected randomly. The survey team settled successively in each selected Bonko. These covered a range of 450 Km. All married women in each selected Bonko who were not pregnant or menstruating participated in the study. Numbers of participant women in the selected Bonkos ranged from 7 to 50. The Bonkos were selected up to the calculated number of women in the tribe. For example we calculated that we needed to sample 270 individuals in the Amaleh tribe. We therefore selected successive Bonkos in the Amaleh tribe until 270 individuals from this tribe were recruited. Our team consisted of one general practitioner and a nurse who trained as an instructor in the university in the obstetrics and gynecology department. An obstetrician-gynecologist observed and checked the observations of the practitioner and nurse. The team supplied some necessary medications and First Aid as required. The chief of the Bonko announced the women of the selected Bonko at least one day before the team settled. When the team arrived in the field of the selected Bonko, all the women would sit together in front of the tent, which was used as the survey clinic and where

the medical equipment was set up. There was some enthusiasm to see our team, because this was the first health project, which many of them had ever encountered. The selected women were interviewed using a standard questionnaire. Interviews took place in Persian or if necessary in the native Turkish dialect of the subjects. The questionnaire consisted of identity and demographic information, family, obstetric, gynecological, and menstrual history, contraceptive use, place of child bearing, smoking habits and economic history. A gynecological examination was administered and signs of maternal morbidity noted. A Pap smear was taken for every woman without bimanual examination or lubricant. A wooden Ayre-type spatula was used and rotated around the cervix twice with firm pressure. We used two parts on the same glass slide, C for the specimen from the ectocervix around the external os, and V portion for the specimen from the upper lateral wall of the vagina. The sample was immediately fixed and labeled with the woman's identification number. The smears were sent to the cytology laboratory of the Shiraz University of Medical Sciences. All smears were seen by one of the reference cytologists. The obstetrician and gynecologist checked all reports. If there was abnormal cytology, the patients were recalled and all necessary diagnoses; treatment or surgery were performed without any charge. If there was infection, the appropriate medicine was prescribed.

3.1.2 Statistical Methods

Since the most commonly observed cytological feature was cervicitis (inflammatory atypia of undetermined origin), the statistical analysis aimed mainly at determining the factors associated with this condition. Cervicitis was classified into four categories: no cervicitis, mild, moderate and severe cervicitis. The cytological criteria for classification are given in section 2.3.3. For univariate analysis, this was further dichotomized to no cervicitis and any cervicitis, and odds ratios calculated as estimates of relative risk of cervicitis. For the

purposes of the univariate analysis, risk factors, which were continuous or multi-level, were dichotomized. For the multivariate analysis, to arrive at a more compact model, we carried out a backward stepwise regression. In this analysis, we used the full information, continuous, and multi-level risk factors (with trend tests where appropriate) and fitted a proportional odds model (*1*) to utilize the information on degree of cervicitis. This is similar to logistic regression but instead of producing odds ratios for disease compared to no disease, it yields proportional odds ratios, which are weighted averages of odds ratios of exceeding each level of the ordered categorical outcome. Thus in our case, for a given risk factor the proportional odds ratio is a weighted average of the odds ratios for any cervicitis compared to none, (*2*) moderate or severe cervicitis compared to mild or none, and (*3*) severe cervicitis compared to mild, moderate or none.

3.2 Results

Table 3-1 shows the basic characteristics of the survey sample. Although there were 1015 women in the survey, some factors were not ascertainable in varying numbers of women. Note that there is a high prevalence of cervicitis, which no dysplasia was observed other than in the two cases of cervical carcinoma in situ, and that this is a population with generally high parity. Cytology results including presence and severity of cervicitis, were available for 1004(99%) women.

Table 3.1: Basic characteristics of survey sample

Variable	Category	No (%)
Age	<20	41(4)
	20-29	228(23)
	30-39	276(27)
	40-49	199(19)
	≥50	217(27)
	Total	961(100)
Menopausal status	Premenopausal	673(67)
	Postmenopausal	326(33)
	Total	999(100)
Parity	0	69(7)
	1-3	172(17)
	4-6	283(28)
	≥7	481(48)
	Total	1006(100)
Cytology result	No abnormal cell	188(19)
	Mild cervicitis	198(20)
	Moderate cervicitis	396(39)
	Severe cervicitis	220(22)
	Carcinoma in situ	2(0.2)
	Total	1004(100)

Table 3-2 shows the univariate results for non-reproductive variables. No significance effects were observed, although there was a suggestive association of cervicitis with late age at marriage.

Table 3.2: Univariate odds ratios-effect of non-reproductive variables on risk of cervicitis

	Case	Non-Case		
Variable	**RF[a] / RF[+]**	**RF[-] / RF**	**OR[b]**	**P[c]**
Age 40+	439/367	99/88	1.07	0.7
Household size 8+	438/315	108/62	1.25	0.2
Formal education	750/64	176/12	1.25	0.25
Smoke cigarette	798/15	18216	0.57	0.3
Smoke hookah	444/369	107/81	1.10	0.6
Land ownership	276/527	52/133	0.74	0.1
Livestock	116/677	29/151	1.12	0.6
High economic score	331/355	69/82	0.90	0.6
BMI 30+	648/88	140/25	0.76	0.3
Age at marriage 21+	648/134	157/21	1.55	0.08
Married for 30+years	571/211	125/53	0.87	0.2

[a] Risk Factor
[b] Odds Ratio
[c] significance

Table 3-3 shows the results for reproductive variables. Significant increases in risk were observed for high parity (in terms of numbers of either pregnancies or deliveries) and history of ever using a neighbour birth assistant. A significantly lower risk was noted for history of ever using a traditional midwife. There was a suggestive association of cervicitis with less frequent sexual intercourse.

Table 3.3: Univariate odds ratio of reproductive variables on risk of cervicitis

Variable	Cases RF[a]/RF+	Non-cases RF-/RF+	OR[b]	P [c]
Age at 1st pregnancy 21+	567/212	140/39	1.34	0.1
4 or more pregnancies	167/646	53/135	1.52	0.02
history of abortion	634/179	153/35	1.23	0.3
4 or more deliveries	181/632	56/132	1.48	0.03
postmenopausal	554/257	119/69	0.80	0.2
polygamy	717/94	166/22	0.99	0.9
intercourse 3+/week	672/130	143/40	0.69	0.09
Intercourse during menstruation	261/540	54/131	0.85	0.4
Oral contraceptive	691/120	163/25	1.13	0.6
BA neighbor	211/602	77/111	1.98	0.0001
BA traditional midwife	724/89	153/35	0.53	0.004
Maternity hospital	689/134	164/24	1.34	0.2
Health house	777/35	182/6	1.36	0.5
Hospital	712/100	169/19	1.24	0.4
Post partum bleeding	739/72	175/13	1.31	0.3
Postpartum fever	712/100	168/20	1.17	0.6
Puerperal infection	780/31	179/9	0.79	0.6
Examined by OB/GYN	600/213	132/56	084	0.3

[a] Risk Factor
[b] Odds Ratio
[c] significance

In the multivariate analysis using the proportional odds model, the variables significant after backward stepwise regression were age (p=0.02), number of deliveries (p=0.001), intercourse during menses (p=0.03), history of ever giving birth in a maternity hospital (p=0.02), and duration of marriage (p=0.05). For age, the risk of severity of cervicitis was greatest in ages 50-59, with lowest risk in ages 19 or less and 60 or more (table 3-4).

There is clearly collinearity of age, parity and duration of marriage. For example, the correlation coefficient between age and duration of marriage was 0.95 . Since these were among the multivariate significant effects identified by the stepwise regression, we have

retained them all in the final model. However, the collinearity probably implies over-adjustment, so results should be interpreted with great caution.

Table 3.4: Adjusted effect of age on degree of cervicitis-frequencies (%) and results of proportional odds modelling

Degree of Cervicitis	Age group					
	>19	20-29	30-39-	40-49	50-59	<60
Non	12(29)	46(21)	41(15)	37(19)	22(15)	29(27)
Mild	8(20)	49(22)	49(18)	42(22)	22(15)	23(21)
Moderate	18(44)	95(43)	120(44)	76(39)	59(38)	27(25)
Severe	3(7)	33(14)	64(23)	40(20)	48(32)	30(27)
OR[a]	1.00	1.59	2.35	1.77	2.36	1.14
POR[b]	1.00	1.31	1.51	0.96	1.96	0.70
95% CI[c]	-	0.65-2.50	0.98-2.33	0.61-1.52	1.08-3.25	0.43-1.15

[a]crude odds ratio for any cervicitis as opposed to none

[b]proportional odds ratio representing risk of increased degree of cervicitis, adjusted for intercourse during menses,history of birth in maternity hospital, and number of deliveries. On an adjusted test for trend, p=0.02

[c]95% confidence interval on the proportional odds ratio

Table 3.5: Adjusted effect of duration of marriage on degree of cervicitis-frequencies(%) and results of proportional odds modelling

Degree of Cervicitis	Duration of marriage			
	0-9	10-19	20-29	30+
Non	47(22)	43(17)	35(17)	53(20)
Mild	42(20)	54(20)	39(18)	43(17)
Moderate	89(42)	118(44)	94(43)	88(33)
Severe	33(16)	53(19)	49(22)	80(30)
OR[a]	1.00	1.50	1.49	1.14
POR[b]	1.00	0.91	0.92	0.73
95% CI[c]	-	0.57-1.44	0.59-1.44	0.40-1.32

[a]crude odds ratio for any cervicitis as opposed to none

[b]proportional odds ratio representing risk of increased degree of cervicitis, adjusted for age, intercourse during menses,history of birth in maternity hospital, and number of deliveries. On an adjusted test for trend, p=0.05

[c]95% confidence interval on the proportional odds ratio

Table 3.6 Adjusted effect of use of maternity hospital on degree of cervicitis-frequencies(%) and results of proportional odds modelling

Degree of Cervicitis	Maternity hospital	
	Never	Ever
Non	164(19)	24(15)
Mild	175(21)	23(15)
Moderate	327(39)	69(44)
Severe	177(21)	42(26)
OR[a]	1.00	1.30
POR[b]	1.00	1.45
95% CI[c]	-	1.04-2.02

[a]crude odds ratio for any cervicitis as opposed to none

[b]proportional odds ratio representing risk of increased degree of cervicitis, adjusted for age, intercourse during menses,history of birth in maternity hospital, and number of deliveries. On an adjusted test for trend, p=0.05

[c]95% confidence interval on the proportional odds ratio

Table 3.7: Adjusted effect of intercourse during menses on degree of cervicitis-frequencies (%) and results of proportional odds modelling

Degree of Cervicitis	Intercourse during menses	
	Never	Ever
Non	54(17)	131(19)
Mild	96(30)	94(14)
Moderate	112(36)	281(42)
Severe	53(17)	165(25)
OR[a]	1.00	0.85
POR[b]	1.00	1.33
95% CI[c]	-	1.02-1.72

[a]crude odds ratio for any cervicitis as opposed to none

[b]proportional odds ratio representing risk of increased degree of cervicitis, adjusted for age, intercourse during menses,history of birth in maternity hospital, and number of deliveries. On an adjusted test for trend, p=0.05

[c]95% confidence interval on the proportional odds ra

Table 3.8: Adjusted effect of number of deliveries on degree of cervicitis-frequencies(%) and results of proportional odds modelling

Degree of Cervicitis	No of deliveries			
	0	1-3	4-6	7+
Non	28(41)	28(17)	54(20)	78(16)
Mild	8(12)	41(24)	57(20)	92(19)
Moderate	20(29)	72(42)	114(40)	190(40)
Severe	12(18)	28(17)	58(20)	121(25)
OR[a]	1.00	3.53	2.97	3.62
POR[b]	1.00	1.52	0.93	1.26
95% CI[c]	-	0.88-2.61	0.62-1.39	0.92-1.72

[a]crude odds ratio for any cervicitis as opposed to none

[b]proportional odds ratio representing risk of increased degree cervicitis, adjusted for age, intercourse during menses,history of birth in maternity hospital, and number of deliveries. On an adjusted test for trend, p=0.05

[c]95% confidence interval on the proportional odds ratio

In the multivariate proportional odds model, risk declined with increasing duration of marriage (Table 3-5). An increased risk was observed for history of birth in maternity hospital(table 3-6). Risk increased with the practice of intercourse during menses (Table 3-7), in contrast to the univariate crude odds ratio result. Although the effect of number of deliveries on risk severity of cervicitis is the most significant of all the variables, in terms of severity of cervicitis in the multivariate model, it seems to reflect an increased risk for any deliveries compared to none, rather than a steady trend (Table 3-8).

3.3 Discussion

The striking result here is the very high prevalence of cervicitis. In this study, more than 80% of the women had cytological evidence of cervicitis. There were two cases of cervical carcinoma in situ (confirmed by biopsy), but other than these two, no dysplasia cases. It should be noted however that severe inflammation renders cervical smear reading for dysplasia difficult. These findings are not unprecedented, as similar results have been found in a study in southern India (*4*) .

Although there was a slight increase in risk of more severe cervicitis with a history of intercourse during menses, the cervicitis does not appear to be solely related to sexual activity. No evidence of any effect of polygamy on the part of the husband was observed (table 3-3), although it should be noted that this was practiced only in 12% of cases in the survey. Also, this is a Muslim population with corresponding traditionally strict lifestyle habits in both men and women (*5*). The increased risk with childbirth suggests that at least one infectious agent causing the cervicitis is contracted at delivery. The significant univariate result of an increased risk associated with use of a neighbour, as birth assistant is consistent with this. The primitive obstetric care available to this population is also consistent with this. In the days when obstetric care was considerably less sophisticated in western Europe, childbirth was a similarly important source of cervical infection. The increased risk associated with use of maternity hospital is unexpected (Table 3-6). This may reflect a prior obstetric problem which predisposes to both cervicitis and seeking the specialist obstetric care provided in the maternity hospital. Results of the proportional odds models are not always straightforward to interpret. For example, significant trends in risk were noted for both duration of marriage and number of deliveries, but no proportional odds ratio significantly differs from the baseline category. This can also happen with trend tests in ordinary logistic regression. The test for trend is more powerful than the test for an individual category's risk differing from that of the baseline category. It should also be noted that the effect of deliveries does not seem to take the form of a smooth trend in any case, but looks more like a difference between no deliveries and any deliveries.

The proportional odds modeling indicate a positive association of intercourse in menses with whereas the crude odds ratio shows a non-significant association. This is because the former

takes into account degree of cervicitis: note that there is a higher proportion with severe cervicitis in those reporting intercourse during menses.

As already stated, the collinearity of age, duration of marriage and parity may mean that inclusion of all three in the same model may constitute over-adjustment. Results should therefore be interpreted tentatively.

The above begs the question as to what are the likely infectious agents responsible for such a high prevalence of cervicitis. In other populations, sexually transmitted agents such as HPV and chlamydia have been implicated (*3,6*). These should be addressed further in this population, it is likely that other agents will be at least partly responsible, since as indicated above, childbirth may be a source infection in this population as well as (or possibly instead of) sexual activity. Bacterial agents should be investigated (*7*). Since it is difficult to speculate on a single agent, which might be responsible for a large proportion of the 81 % positive cervicitis cases, a starting point might be to test for bacterial vaginosis, since there is a simple test available which is applicable in the field. This will be dealt with in later chapters, along with repeat cytological assessment of cervicitis, to ascertain persistence of the inflammation, and testing of other populations using the same cytology service (Cytology Department, Shiraz University of Medical Sciences), to ascertain that the high rate of cervicitis is not simply a result of diagnostic practice. It is also important to perform more detailed analysis of birth history data, including places of giving birth and nature of birth assistants, taking account of the total number of births for each individual. Since the publication of impressive results linking HPV to cervical cancer and cervical neoplasia (*8,9*), it is easy to overlook the other potential causal pathways. There is evidence that the inflammatory process as manifested by a diagnosis of cervicitis is at least part of another causal pathway(perhaps related , in that HPV is one of several potential sources of the inflammation). Certainly,

dysplasia has been found in conjunction with moderate to severe inflammation (*10*). Further investigation of this population with such high rates of inflammation gives a unique opportunity for understanding of less well-research aspects of cervical pathology

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Chapter 4

Cervical Pathology and Infection in Nomadic and Non-nomadic women in Southern Iran – three more recent surveys

4.1 Introduction

Gynaecological infections are common worldwide. The problem is especially serious in developing countries, where there are inadequate health services to detect and treat these infections. The problem is complicated further by the lack of diagnostic facilities (*1*).

Reproductive tract infections constitute a silent epidemic, which has a considerable effect on women's lives. Each year, thousands of women die needlessly from the consequences of these infections, including cervical cancer, ectopic pregnancy, acute and chronic infections of the uterus and the fallopian tubes, and puerperal infections. In many cases , this happens because they receive medical attention too late, if at all. Ironically early diagnosis of and treatment for many reproductive tract infections do not require high technology health care (*2*).

Vaginitis and cervicitis are common gynaecologic problems with potentially serious sequelae in sexually active females. Screening tests for gonococcal and chlamydial cervicitis have been successfully implemented in many clinics in developed countries. However, clinics in areas with limited resources may have difficulty implementing universal screening for these infections (*3*).

Cervicitis may be produced by a wide variety of aetiological agents with the cervix being involved either as the site of a primary lesion or as a secondary aspect of a systemic illness (*4*). It has been associated with bacterial vaginosis (BV). Bacterial vaginosis is a

polymicrobial condition in which a decrease in vaginal acidity and in the concentration of lactobacilli is accompanied by an increase of 100-fold or more in the concentration of other microorganisms. No single microorganism is detected in all women with bacterial vaginosis. In clinics for sexually transmitted diseases the reported prevalence of BV has been between 24% and 37%. The epidemiology of the condition has some of the characteristics of a sexually transmitted disease and it is associated with increasing age and the presence of Neisseria gonorrhoea and Chlamydia trachomatis (*5*).

In the last chapter, we observed a high prevalence of cervicitis among Qashgha'i nomadic women in southern Iran. It is of some importance to the health of this population to establish the organic aetiology of the cervicitis in this population. This involves comparison with other populations from the same area and investigation of association of cervicitis with various infections. We therefore report cervical pathology and infection in nomadic and non-nomadic women in Southern Iran and also the relationship between them. We study these in three high-risk populations for cervicitis: the women of the Qashgha'i nomadic tribe, the Lor nomadic tribe and the non-nomadic urban population in southern Iran.

4.2 Methodology

4.2.1 Subjects and Data Collection

In 1996-1997 surveys were carried out of 709 married women members of the Qashgha'i tribe, 274 married women members of the Mamasani Lor tribe and 388 consecutive urban married women attending a large central OB-GYN clinic in Fars province, Southern Iran. As in the previous survey of Qashgha'i women, the women of the Qashgha'i and the Lor population were selected by stratified random sampling, in two tiers to give the women in proportions representative of the six tribes of the Qashgha'i, and of clans within the tribes,

and of the four tribes of the Lor population. Again as in chapter 3, the sample units were the Bonko. As before, the survey team consisted of one general practitioner, one midwife and one epidemiologist. An obstetrician-gynecologist checked the observations of the practitioner and midwife. The interview questionnaire was the same as the past Qashgha'i survey (chapter 3). A gynecological examination was administered and a Pap-smear was taken as in the previous survey. Vaginal secretions were collected for assessing bacterial vaginosis by Gram staining.

Figures 4.1 – 4.5 show various aspects of the fieldwork.

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Figure 4.1: Lur women waiting to be seen at the clinic,
this tent is usually used as the class room

Figure 4.2: Oashgha'I women waiting to be seen at the clinic, this tent is usually used as the class room

Figure 4.3: Administering the questionnaire inside the clinic

Figure 4.4: Undertaking a gynecological exam

Figure 4.5: A general practitioner dispensing medication from the small portable pharmacy, the picture also show a cold box used for storing blood samples and smears

The smears were sent to the cytology and microbiology laboratories of the Shiraz University of Medical Sciences. All smears were seen by one of the reference cytologists

and microbiologist. The obstetrician and gynecologist checked all reports. If there was abnormal cytology or signs of bacterial vaginosis, the patients were recalled and all necessary diagnoses, treatment and surgery were done without any charge. If there was infection, the appropriate medicine was prescribed.

Cervicitis was classified into four categories:

- No Cervicitis
- Mild Cervicitis
- Moderate Cervicitis
- Severe Cervicitis

It was scored from the cytology as follows:

- Mild cervicitis denotes PMNs observed in less than 25 % of microscope fields
- Moderate cervicitis denotes PMNs found 25-75 % of fields
- Severe cervicitis denotes PMNs found in more than 75% of fields (Figures 4.6 - 4.9).

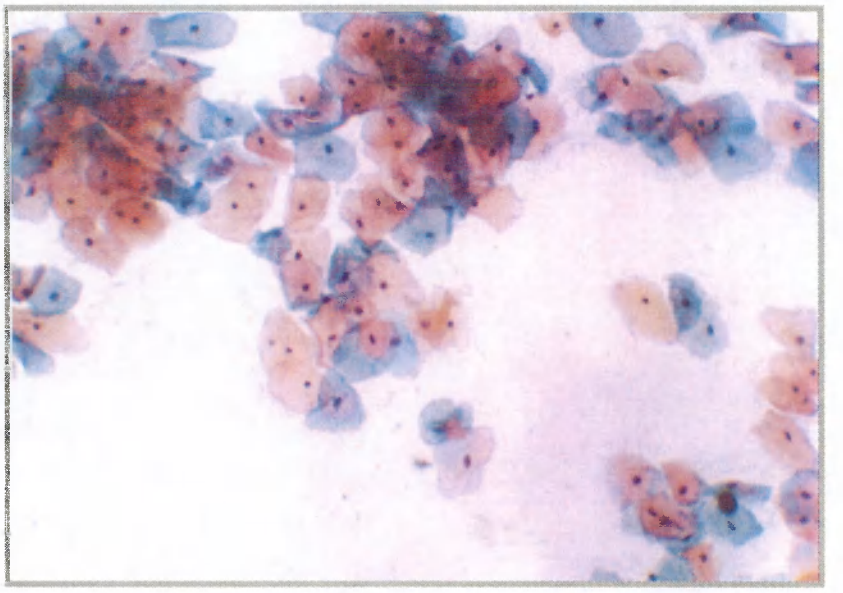

Figure 4.6: Cytology of typical normal cells of the cervix

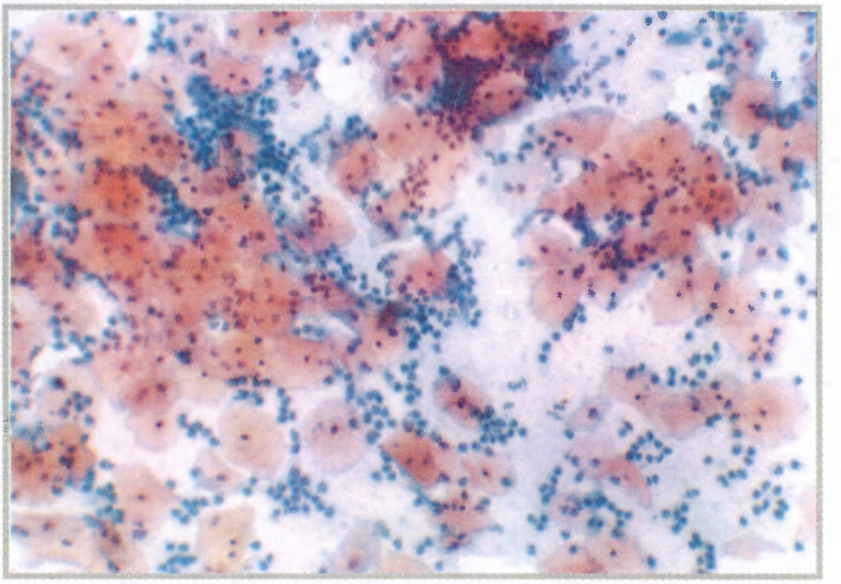

Figure 4.7: Cytology of mild inflammation

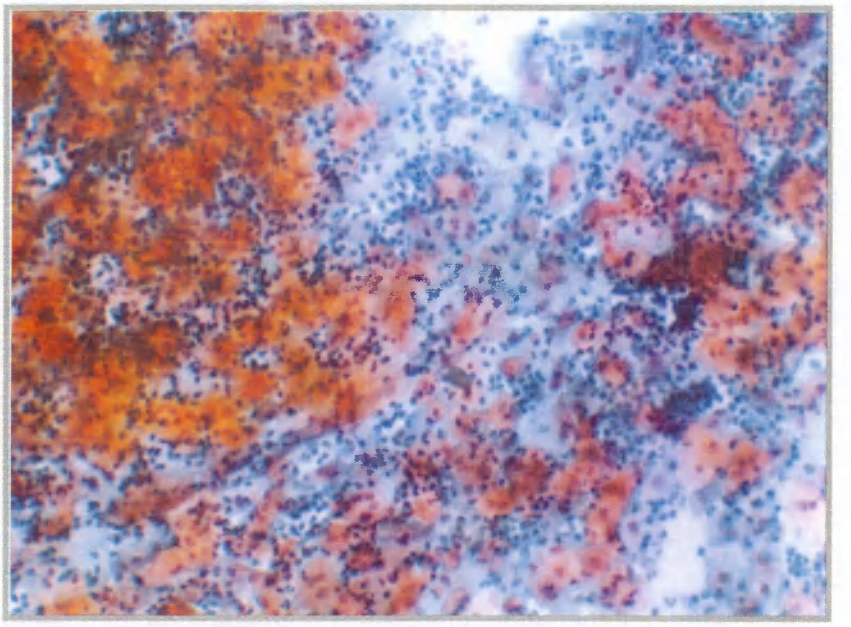

Figure 4.8: Cytology of typical moderate inflammation

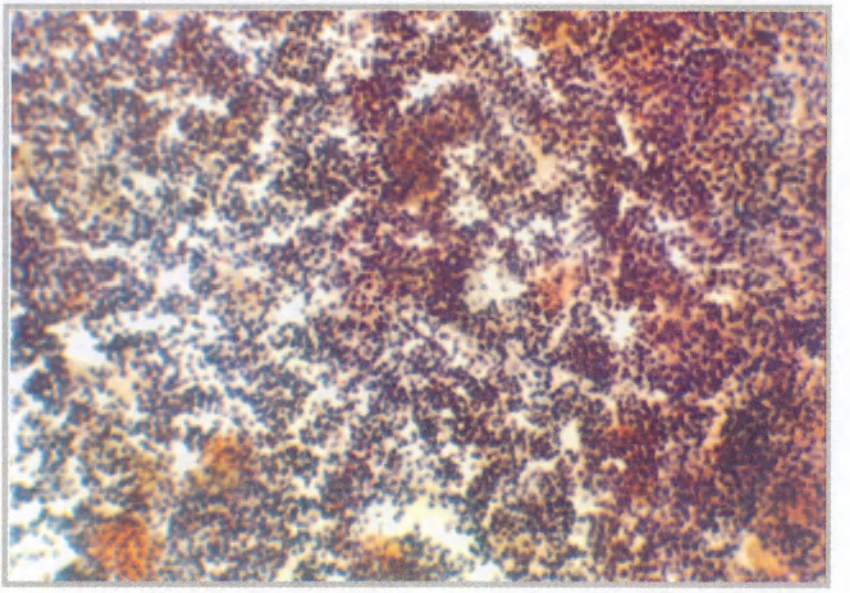

Figure 4.9: Cytology of severe inflammation

Bacterial vaginosis was scored on the basis of the concentration of three organisms as shown in table 4.1, then graded into 2 groups, normal or bacterial vaginosis. A score of 4 or more is classified as a case of BV (*6*). If microbiologist scored 3+ for Lactobacillus morphotypes, 2+ for Gardnerella and Bacteroides spp. morphootype, and 3+ for Curved gram variables rods the woman would have a total score of eight. This woman had BV according to the Nugent score in table 4.1.

Reproductive morbidity was defined as any morbidity or dysfunction of the reproductive tract, or any morbidity which is a consequence of reproductive behavior including pregnancy, abortion, childbirth, or sexual behavior (*7*). Reproductive morbidity was diagnosed by clinical examination, including inspection with a vaginal speculum as the diagnostic instrument .

Table 4.1: Scoring system for Gram stained vaginal smears[a]

Score[b]	Lactobacillus morphotypes	Gardnerella and Bacteroides spp. morphotype	Curved gram Variables rods
0	4+	0	0
1	3+	1+	1+ or 2+
2	2+	2+	3+ or 4+
3	1+	3+	
4	0	4+	

a: morphotypes are scored as the average number seem per oil immersion field note that less weight is given to curved gram-variable rods. Total score=lactobacilli + Gardnerella and Bacteroides spp. + curved rods
b: 0, No morphotypes present; 1,< 1 morphotypes present; 2. 1 to 4 morphotypes present; 3, 5 to 30 morphotypes present; 4, 30 or more morphotypes present (the difference between 0 morphotypes and <1 morphotype arises because these are averages per immersion field).

4.2.2 Data preparation

Partial coding was carried out at the time of the interview ready for data entry. Data entry was verified and errors corrected. Once the data had been entered simple frequency checks were performed to identify values outside accepted ranges.

4.2.3 Statistical Methods

SAS 6.12 was used for all statistical analysis. Logistic regression was used to assess effects on risk of cervicitis, bacterial vaginosis and reproductive morbidity. Odds ratios were calculated from logistic regression (*8*) as estimates of relative risk of cervicitis and bacterial vaginosis. In addition to the reproductive and non-reproductive factors in the questionnaire we also considered the clinical observations of reproductive morbidity as potential covariates. For multivariate analysis, to arrive at a compact model, we carried out a backward stepwise regression. We also calculated the attributable risk of cervicitis associated with bacterial vaginosis (*8*). For simplicity of presentation, aside from the variables which were most predictive of cervicitis in the first survey, and whose effects we confirm in the present surveys, the risk factors were dichotomized for analysis.

Sensitivity, specificity, positive predictive value, negative predictive value and the percentage of agreement were used to compare clinical observation of cervicitis and erosion to the result of Pap smears. Table 4.2 provides definitions of these indicators. Sensitivity and specificity are affected by the cutoff point selected to indicate a positive clinical observation of a sign. Ideally, both sensitivity and specificity must be high, but usually, for any cutoff point, sensitivity is sacrificed for specificity and vice-versa (*9*). The predictive value of clinical observations is important because it provides information about the relative magnitude of accurate positive and negative predictions from clinical observations. The percentage of agreement indicates overall efficiency in representing agreement between clinical observations and the Pap test. The Kappa statistic is also used as a summary measure of agreement because it improves upon the latter measure by discounting the proportion of agreement that is to be expected according to chance (*10*).

Table 4.2: Comparison of clinical observations with Pap test of presence of disease

Clinical Observation	Pap Smear Test		
	Yes	No	Total
Yes	a	b	a+b
No	c	d	c+d
Total	a+c	b+d	n

Sensitivity = ability of a symptom to lead to detection of disease if present (a /a + c).

Specificity = ability of a symptom to cause the ruling out of disease if not present (d / b + d).

Positive predictive value = percent of those who reported a symptom and for whom the disease is present (a/a+b).

Negative predictive value=percent of those who did not report a symptom and for whom the disease is not present (d/c + d).

Percentage of agreement = percent of those whose clinical observation is consistent with the presence of disease (a+d /n).

Kappa statistic= percentage of agreement discounting the proportion of agreement that is to be expected according to chance alone (po-pe/1-pe), where po = percentage of agreement and pe =expected agreement according to chance (10).

4.3 Results

The results below are divided into four parts: the first part demonstrates the demographic information and the cytology results and the association with cervicitis; the second shows the effects of the vaginitis or BV as determined by the gram stained vaginal smear; the third shows the relationship with reproductive morbidity; and the fourth deals with the

association between the three conditions. For analysis of effects on cervicitis, the first priority was to attempt to validate the effects of the risk factors identified in the last survey (see chapter 3) of the Qashgha'i. These factors are age, duration of marriage, number of deliveries, use of maternity hospital, and history of intercourse during menses.

4.3.1 Basic information, Cytology results and effects on cervicitis

Some basic information on non-reproductive factors in women in the surveys is given in table 4.3. The urban women were significantly more likely to have smaller households, to be younger, and less likely to smoke the hookah than the Qashgha'i and Lor tribeswomen ($p < 0.001$ in all cases). The women of both tribes were more likely than the urban women to be married to polygamous husbands ($p<0.001$). The economic variable based on livestock was not applicable to the urban women. The Qashgha'i were of higher economic status than the Lor ($p <0.001$).

Table 4.3: Frequency and percentage of selected non-reproductive variables in the survey populations

Variables		Population								
		Qashgha'i[a]		Lor		Urban		X^2	df	p
		No	(%)	No	(%)	No	(%)			
Household size	#4	152	18	54	20	162	42			
	5-7	333	40	108	40	163	42			
	8-10	274	33	92	34	55	14			
	∃11	79	9	16	6	8	2	121	6	0 .001
Age	#29	245	29	73	27	132	34			
	30-39	254	30	95	36	150	39			
	40-49	195	23	55	21	71	18			
	∃50	142	17	43	16	34	9	24	6	0 .001
Smoke cigarette	Yes	19	2	6	2	7	2			
	No	818	98	263	98	374	98	0.25	2	0.87
Smoke hookah	Yes	276	36	59	25	26	7			
	No	487	64	175	75	344	93	109	2	0.001
Polygamy of husband	Yes	75	9	23	9	12	3			
	No	762	91	244	91	373	97	24	3	0.001
Economic Status	Low	570	73	220	88	-	-			
	Intermediate	122	17	23	9	-	-			
	High	78	10	7	3	-	-	22	2	0.001

[a]survey in 1997

The details of age at marriage, age at first pregnancy, number of pregnancies, and number of deliveries are given in table 4.4. About half of the women in the Lor tribe got married at the age of 15 or younger. On the other hand, the majority of women in all three populations got married when they were 20 or younger. There is a significant difference between the populations in the age at marriage ($p<0.001$). Whilst approximately half of the women in each of the three populations became pregnant before 20 years old, there is still a significant difference in age at first pregnancy between the populations ($p = 0.05$). These are populations with generally high parity, and the tribeswomen had significantly higher parity than the urban women.

Table 4.4 Frequency and percentage of reproductive variables in the survey populations

Variables		Population						X^2	df	p
		Qashgha'i[a]		Lor		Urban				
		No	(%)	No	(%)	No	(%)			
Age at Marriage	≤15	295	36	134	50	125	32			
	16-20	416	50	116	44	177	46			
	21-25	102	12	13	5	75	19			
	≥26	19	2	3	1	11	3	46	6	0 .001
Age at first Pregnancies	≤15	197	24	81	30	95	24			
	16-20	428	51	145	54	193	50			
	21-25	168	20	35	13	76	20			
	≥26	46	5	9	3	24	6	12	6	0 .05
No of Pregnancies	0	31	4	15	5	22	6			
	1-3	162	19	46	17	176	45			
	4-6	235	28	94	35	126	32			
	≥7	411	49	115	43	64	17	158	6	0.001
No of Deliveries	0	33	4	15	5	26	7			
	1-3	180	21	48	18	201	52			
	4-6	250	30	96	36	120	31			
	≥7	376	45	111	41	41	10	19	6	0.001

[a]survey in 1997

Table 4.5 Frequency and percentage of cytology results and findings in the survey populations

Variables		Population						X^2	df	p
		Qashgha'i[a]		Lor		Urban				
		No	(%)	No	(%)	No	(%)			
Results:	Atypical	436	53	134	52	236	74			
	Normal	384	47	124	48	81	26	46	2	0 .001
Findings:	Yes	177	22	39	15	70	22			
Metaplastic cell	No	644	78	219	85	247	78	5.6	2	0.06
Keratinized cell	Yes	32	4	2	0.7	4	3			
	No	788	96	256	99.3	115	97	6	2	0.04
Hyperkeratinized	Yes	40	4	11	4	5	3			
cell	No	782	96	247	96	155	97	1	2	0.6
Histiocytes	Yes	736	90	212	85	80	33			
	No	80	10	38	15	157	66	357	2	0.001
P.M.N.	Yes	765	94	232	93	84	35			
leukocytes	No	51	6	18	7	153	65	462	2	0.001
Trichomonas	Yes	25	3	2	1	2	1			
	No	797	97	256	99	314	99	9	2	0.01
Monilia	Yes	25	3	6	2	12	5			
	No	797	97	252	98	231	95	3	2	0.2

[a]survey in 1997

The cytology results and the findings from the cervicovaginal smears are summarized in the table 4.5. The presence of atypical cells was noted in about 50 % of tribeswomen and 74% of urban women. The most important finding in this survey is the presence of inflammation, as shown in table 4.6. The highest prevalence of cervicitis is in the Qashgha'i tribe. The other two populations also have high prevalence of cervicitis. About 80 % of the cases of cervicitis are mild to moderate in severity.

Table 4.6 Frequency and percentage of inflammatory epithelial changes in cervical cytology in the survey populations

Variables		Population						X^2	df	p
		Qashgha'i[a]		Lor		Urban				
		No	(%)	No	(%)	No	(%)			
Cervicitis	Yes	726	88	213	83	223	71			
	No	96	12	45	17	92	29	50	2	0.001
Degree of Cervicitis	Mild	250	30	78	30	25	8			
	Moderate	429	52	128	50	190	60			
	Severe	47	6	7	3	8	3	101	6	0.001

[a]survey in 1997

Table 4.7 shows that the risk of cervicitis is greatest in the age group 30-39 for the Qashgha'i and Lor populations, with a lower risk for ages 60 or more in the three populations.

Table 4.7: The effect of age on risk of cervicitis and frequencies (%)in the survey populations

Population	Degree of cervicitis	Age				
		<29	30-39	40-49	50-59	60+
Qashgha'i[a]	**None**	28(12)	16(6)	25(13)	14(18)	12(22)
	Mild	74(30)	88(35)	60(31)	15(19)	13(24)
	Moderate	134(55)	137(55)	97(5)	39(49)	22(40)
	Severe	7(3)	9(4)	10(5)	11(14)	8(15)
	OR	1.00	1.90	0.86	0.60	0.46
	95% CI	-	1.00-3.61	0.48-1.54	0.30-1.21	0.22-0.98
	Significant	0.001	-	-	-	-
Lor	**None**	13(18)	12(13)	11(21)	4(18)	12(22)
	Mild	20(30)	29(32)	12(23)	3(14)	13(24)
	Moderate	36(15)	45(50)	29(56)	14(64)	22(40)
	Severe	1(2)	4(4)	0(0)	1(5)	8(15)
	OR	1.00	1.46	0.85	1.02	0.68
	95% CI	-	0.63-3.48	0.34-2.08	0.29-3.54	0.21-2.22
	Significant	0.04	-	-	-	-
Urban	**None**	30(29)	36(28)	18(32)	6(32)	2(50)
	Mild	11(11)	9(7)	5(9)	0(0)	0(0)
	Moderate	64(60)	79(61)	34(60)	11(58)	2(50)
	Severe	1(1)	4(4)	0(0)	2(11)	0(0)
	OR	1.00	1.01	0.85	0.85	0.39
	95% CI	-	0.57-1.48	0.42-1.72	0.29-2.45	0.05-2.93
	Significant	0.34	-	-	-	-

A women who has been married for a duration of 10-19 years has the greater risk in both the Qashgha'i and the Lor, but in the urban group the higher risk is after 20-29 years of marriage (table 4.8)

Table 4.8: The effect of duration of marriage on risk of cervicitis and frequencies(%)in the survey populations

Population	Degree of cervicitis	Duration of marriage (year)			
		0-9	10-19	20-29	30+
Qashgha'i[a]	**None**	29(14)	16(6)	30(15)	24(14)
	Mild	53(28)	93(35)	56(28)	48(28)
	Moderate	99(53)	149(56)	102(51)	79(46)
	Severe	9(5)	7(3)	12(6)	19(11)
	OR	1.00	2.51	0.91	0.98
	95% CI	-	1.30-4.83	0.52-1.61	0.54-1.79
	Significant	0.001	-	-	-
Lor	**None**	10(21)	12(12)	11(19)	12(22)
	Mild	18(38)	28(29)	15(26)	17(22)
	Moderate	19(40)	54(56)	31(53)	24(44)
	Severe	1(2)	3(3)	1(2)	2(4)
	OR	1.00	1.86	1.12	0.94
	95% CI	-	0.74-4.68	0.43-2.93	0.36-2.42
	Significant	0.67	-	-	-
Urban	**None**	27(30)	135(28)	14(23)	16(38)
	Mild	6(7)	13(11)	4(7)	2(5)
	Moderate	55(62)	71(58)	42(69)	22(52)
	Severe	1(1)	4(3)	1(2)	2(5)
	OR	1.00	1.01	1.46	0.71
	95% CI	-	0.60-1.99	0.69-3.09	0.33-1.53
	Significant	0.61	-	-	-

[a]survey in 1997

An increased risk was observed for women in the Lor tribe and also for the Qashgha'i with an increasing number of deliveries. (Table 4.9).

The effect of number of deliveries on the risk of any cervicitis in the Qashga'ii second survey (Table 4.9) was similar, although slightly attenuated, to that observed in the first survey (Table 3.3). Both suggest that the major difference in risk is between the nulliparous and the parous women. Also, in both surveys, similarly high levels of parity were observed.

Table 4.9: The effect of number of deliveries on risk of cervicitis and frequencies (%)in the survey populations

Population	Degree of cervicitis	Number of delivery			
		0	1-3	4-6	7+
Qashgha'i[a]	**None**	7(22)	22(12)	22(9)	45(12)
	Mild	11(34)	53(30)	82(33)	10(28)
	Moderate	13(41)	98(55)	128(52)	190(52)
	Severe	1(3)	6(3)	13(5)	27(7)
	OR	1.00	2.00	2.84	2.00
	95% CI	-	0.77-5.16	1.10-7.30	0.81-4.88
	Significant	0.28	-	-	-
Lor	**None**	10(67)	8(17)	5(6)	22(21)
	Mild	2(13)	15(33)	29(32)	32(30)
	Moderate	3(20)	22(48)	52(58)	51(48)
	Severe	0(0)	1(2)	4(4)	2(2)
	OR	1.00	9.50	34.00	7.73
	95% CI	-	2.54-35.45	8.37-138.17	2.40-24.93
	Significant	0.001	-	-	-
Urban	**None**	2(29)	44(27)	31(30)	8(30)
	Mild	0(0)	19(12)	6(6)	0(0)
	Moderate	12(57)	95(59)	63(62)	20(67)
	Severe	1(5)	4(2)	2(2)	1(3)
	OR	1.00	1.64	1.41	1.44
	95% CI	-	0.64-4.25	0.53-3.74	0.44-4.66
	Significant	0.16	-	-	-

[a]survey in 1997

Table 4.10: The effect of use of maternity hospital on risk of cervicitis and frequencies(%)in the survey populations

Population	Degree of cervicitis	Maternity hospital	
		Never used	Ever used
Qashgha'i	**None**	26(8)	70(14)
	Mild	114(35)	134(27)
	Moderate	170(52)	256(52)
	Severe	16(5)	31(6)
	OR	1.00	1.91
	95% CI	-	1.19-3.08
	Significant	0.01	-
Lor	**None**	12(13)	33(20)
	Mild	27(28)	51(31)
	Moderate	51(54)	76(50)
	Severe	5(5)	2(1)
	OR	1.00	1.76
	95% CI	-	0.86-3.62
	Significant	0.09	-
Urban	**None**	18(23)	73(31)
	Mild	5(6)	20(9)
	Moderate	57(71)	132(57)
	Severe	0(0)	8(3)
	OR	1.00	1.57
	95% CI	-	0.86-2.84
	Significant	0.003	-

[a]survey in 1997

An increased risk was associated with a history of birth in a maternity hospital for all three populations. Results are shown in table 4.10.

The risk of cervicitis was increased by the practice of intercourse during menses in the urban population, but this was not significant, and in the other populations no such effect was observed (table 4.11).

The results of these surveys are mostly consistent with respect to the risk factors identified in the first survey, with two notable exceptions. The effects of age and duration of marriage were less prominent in the urban women, and the effect of intercourse during menses on severity of cervicitis was not confirmed.

Table 4.11: The effect of intercourse during menses on risk of cervicitis and frequencies (%)in the survey populations

Population	Degree of cervicitis	Intercourse during menses	
		No	Yes
Qashgha'i[a]	None	67(12)	28(12)
	Mild	184(32)	62(27)
	Moderate	294(51)	131(56)
	Severe	34(6)	13(6)
	OR	1.00	0.96
	95% CI	-	0.60-1.54
	Significant	0.47	-
Lor	None	32(17)	13(18)
	Mild	58(32)	19(27)
	Moderate	87(47)	39(55)
	Severe	7(4)	0(0)
	OR	1.00	0.94
	95% CI	-	0.46-1.91
	Significant	0.23	-
Urban	None	65(32)	25(24)
	Mild	15(7)	10(10)
	Moderate	119(58)	67(65)
	Severe	7(3)	1(1)
	OR	1.00	1.43
	95% CI	-	0.83-2.46
	Significant	0.13	-

[a]survey in 1997

Table 4.12 shows the univariate effects on risk of cervicitis for non-reproductive variables. There was a suggestive association of a lower risk of cervicitis associated with age over forty in the Qashgha'i tribe. No other significant effects were observed.

Table4.12: Univariate odds ratio estimates of effect of non-reproductive variables on risk of cervicitis in the survey populations

Variables	Population								
	Qashgha'i[a]			Lor			Urban		
	OR[b]	P(%)[c]	P[d]	OR	P(%)	P	OR	P(%)	P
Age 40+	0.52	40	0.09	0.68	37	0.2	0.81	25	0.4
Household size 8+	1.20	42	0.4	1.15	20	0.7	0.76	16	0.4
Formal education	1.18	17	0.5	1.69	19	0.2	1.32	58	0.2
Smoke cigarette	0.70	2	0.6	1.21	2	0.2	1.21	1	0.8
Smoke hookah	0.75	36	0.2	2.01	25	0.1	0.58	7	0.2
High economic score	1.06	25	0.8	0.82	12	0.6	-	-	-
Age at marriage 21+	0.66	16	0.1	0.83	8	0.7	0.75	22	0.3
Married for 30+ years	0.75	21	0.2	0.70	21	0.3	0.62	13	0.1

[a]survey in 1997
[b]crude odds ratio for any cervicitis as opposed to none
[c]prevalence(%) of factor in the survey population
[d]significance

Table 4.13 shows the results for reproductive variables. Significant or borderline significant increases in risk were observed for use of contraceptive pill at the time of study ($p = 0.06$), use of any contraception at the time of study ($p = 0.05$), and delivery at maternity hospital and a significantly lower risk was noted with postmenopausal status in the Qashgha'ii tribe ($p = 0.01$).

The Lor population showed significant increases in risk with high parity, in terms of numbers or either pregnancies ($p = 0.003$) or deliveries ($p = 0.004$), previous use of contraception pill($p = 0.03$), use of any contraception($p = 0.01$), and history of ever using a traditional midwife or neighbor as a birth assistant($p = 0.01$). Surprisingly an almost significant decrease in risk was observed in those whose husbands had more than one wife ($p = 0.06$).

In the urban population, significant increases in risk were observed for use of contraceptive pill either before ($p = 0.01$) or during ($p = 0.04$) the study. There was a suggestive association of cervicitis with frequent sexual intercourse ($p = 0.09$).

In the Qashga'ii second survey, similar qualitative results as in the first survey were observed for numbers of pregnancies and deliveries, and use of maternity hospital, although exact OR's and significance levels inevitably differed. However, the effects of use of neighbor or traditional midwife as birth assistant observed in the first survey were not replicated in the second.

Table 4.13: Univariate odds ratios effect of reproductive variables on risk of cervicitis in the survey populations

Variables	Population								
	Qashgha'i[a]			Lor			Urban		
	OR[b]	P(%)[c]	P[d]	OR	P(%)	P	OR	P(%)	P
Age at first pregnancy 21+	0.96	24	0.9	0.83	14	0.6	0.86	24	0.6
4 or more pregnancies	1.80	78	0.4	2.79	77	0.003	0.82	50	0.4
History of abortion	0.76	21	0.2	0.81	17	0.6	0.76	28	0.3
4 or more deliveries	1.29	74	0.2	2.63	76	0.004	0.91	41	0.7
Postmenopausal	0.54	20	0.01	0.98	17	0.9	-	-	-
Polygamy	0.64	9	0.1	0.41	7	0.06	0.60	3	0.4
Intercourse 3+ time/week	1.04	18	0.8	0.83	26	0.6	1.56	36	0.09
Intercourse in menses	1.03	30	0.8	1.01	29	0.9	0.71	35	0.1
Pill (before)	1.26	31	0.3	2.06	50	0.03	1.78	40	0.01
Pill (now)	1.75	22	0.06	1.10	19	0.8	2.48	12	0.04
Contraception (any-now)	1.52	50	0.05	2.19	56	0.01	1.35	74	0.2
Birth in hospital	1.00	9	0.9	3.13	11	0.1	0.92	71	0.7
Birth in maternity hospital	1.91	40	0.006	1.76	37	0.1	1.57	26	0.1
BA[e] traditional midwife	1.03	61	0.8	0.93	41	0.8	-	-	-
BA neighbour	0.83	18	0.5	1.94	44	0.05	-	-	-

[a]survey in 1997
[b]crude odds ratio for any cervicitis as opposed to non
[c]prevalence(%) of factor in the survey population
[d]significance
[e]birth assistant

Table 4.14 shows the multivariate backward stepwise regression analysis for predictors of cervicitis. In Qashgha'i significant or borderline significant factors were a decreased risk associated with age over forty (p = 004) and of postpartum bleeding (p = 0.09). In the Lor tribe the predictors of cervicitis were increased risk with more than four pregnancies (p = 0.01). In urban women, the risk of cervicitis was increased with use of oral contraceptive previously (p = 0.03) or at the time of study (p = 0.01).

Table 4.14: Backward stepwise regression results for predictors of cervicitis in each survey population

Sample	RF[a]	Category	Cervicitis		OR[b]	95% CI[c]
			NO	Yes		
Qashgha'i	Postpartum bleeding	No	58(11)	677(89)	1.00	-
		Yes	11(20)	45(80)	0.55	0.27 – 1.11
	Age 40+	No	44(9)	449(91)	1.00	-
		Yes	51(16)	275(84)	0.48	0.29 – 0.79
Lor	Pregnancy 4+	No	18(30)	41(70)	1.00	-
		Yes	27(14)	172(86)	2.51	1.24 – 5.08
	Contraceptive (any)	No	28(24)	86(76)	1.00	-
		Yes	18(12)	126(83)	1.88	0.95 – 3.69
Urban	Oral contraceptive (now)	No	86(31)	190(69)	1.00	-
		Yes	6(15)	33(85)	1.96	1.15 – 3.33
	Oral contraceptive (previously)	No	64(34)	124(66)	1.00	-
		Yes	27(22)	98(78)	2.68	1.07 – 6.70

[a]risk factor
[b]odds ratio
[c]confidence interval

4.3.2 Gram stained vaginal smear results

Bacterial vaginosis was detected in 51% of Qashgha'i, 49% in Lor and 37% in urban studied women, significant differences were found in prevalence of bacterial vaginosis between these three populations ($p < 0.001$). The organisms that may be associated with the bacterial vaginosis, are shown in table 4.15. The comparison of BV between populations is not independent of those of lactobacilli, Gardnerella and curved gram variable rod, since the latter three are scoring components of the first.

Table 4.15: Frequency and proportion of vaginal bacteria in the survey population

Variables		Population								
		Qashgha'i[a]		Lor		Urban		X^2	df	p
		No	(%)	No	(%)	No	(%)			
Bacterial Vaginosis[b]	Normal	351	49	124	51	131	63			
	Intermediate	32	5	28	12	14	7			
	Severe	327	46	89	37	63	30	31	4	0.001
Lactobacillus	None	326	46	87	36	62	30			
	≤4	40	5	36	15	30	14			
	5-30	57	8	18	7	28	14			
	>30	290	41	100	42	88	42	42	6	0.001
Gardnerella Bacteroides	Yes	370	52	116	48	74	36			
	No	343	48	125	52	34	64	17	2	0.001
Curved Gram Variable rod	Yes	22	3	19	8	23	11			
	No	691	97	222	92	185	89	23	2	0.001
Yeast	Yes	54	7.5	15	6	23	11			
	No	659	92.5	226	94	185	89	3.8	2	0.14
Pseudohyphae	Yes	7	1	3	1	6	3			
	No	702	99	233	99	201	97	4	2	0.01
G^- Diplococci (presumptively GC)-	Yes	50	7	17	7	6	3			
	No	663	93	224	93	202	97	5	2	0.08
G^+ Cocci in Chain & cluster	Yes	51	7	17	7	10	5			
	No	653	93	218	93	197	95	1.5	2	0.46
G^- Rod (possible enteric bacteria)	Yes	75	11	12	5	40	20			
	No	627	89	222	96	165	80	23	20	0.001
Diphtheroid	Yes	37	5	24	10	19	9			
	No	676	95	217	90	189	91	8	2	0.015
PMNs[d]	Yes	61	9	19	8	35	17			
	No	656	91	222	92	173	83	14	2	0.001
Clue cell	Yes	23	3	11	5	8	4			
	No	690	97	230	95	200	96	1	2	0.6

[a]survey in 1997
[b]Total score=lactobacilli+Gardnerella and Bacteroids spp+curved rods. Interpret total score as follows: 0 to 3, normal; 4 to 6, intermediate; ∃7, severe BV
cG-cocci
[d]polymorphonuclear cell

Gardnerella bacteroides is the most prevalent bacteria that defines bacterial vaginosis. For age, the risk of bacterial vaginosis was greatest in women 50 years or older and with lowest risk in ages 29 or less in the women of Qashgha'i and Lor population. For urban women, the risk of bacterial vaginosis tended to be higher in women aged over 40, but there was no significant effect.

Table 4.16: The effect of age on risk of bacterial vaginosis and frequencies (%) in the survey populations

Population	Bacterial Vaginosis	Age group			
		<29	30-39	40-49	50-59
Qashgha'i[a]	No	133(60)	119(55)	75(46)	23(23)
	Yes	90(40)	99(45)	89(54)	79(77)
	OR	1.00	1.22	1.75	5.07
	95% CI	-	0.84-1.79	1.16-2.63	2.97-8.67
	Significant	0.001	-	-	-
Lor	No	32(47)	53(61)	29(59)	4(18)
	Yes	36(53)	34(39)	20(51)	3(14)
	OR	1.00	0.57	0.61	3.30
	95% CI	-	0.30-1.08	0.29-1.28	1.26-8.63
	Significant	0.001	-	-	-
Urban	No	40(63)	63(63)	14(50)	8(53)
	Yes	23(37)	37(37)	15(50)	7(47)
	OR	1.00	1.02	1.73	1.52
	95% CI	-	0.53-1.94	0.72-4.19	0.48-4.74
	Significant	0.53	-	-	-

[a]survey in 1997

Table 4.17 shows the univariate results for non-reproductive variables on risk of bacterial vaginosis. In the Qashgha'i significant increases in risk were observed with age over forty(p=0.001), having been married for more than 30 years(p=0.001) and significant lower risk was noted for history of formal education (p=0.001). In the Lor population, a significantly higher risk was noted for having been married more than 30 years (p = 0.001). No significant effects were observed in the urban population.

Table 4.17: Univariate odds ratio estimates for non-reproductive variables on risk of bacterial vaginosis in each survey population

Variables	Population								
	Qashgha'i[a]			Lor			Urban		
	OR[b]	P(%)[c]	P[d]	OR	P(%)	P	OR	P(%)	P
Age 40+	2.32	38	0.001	1.53	37	0.1	1.64	22	0.1
Household size 8+	1.15	43	0.33	1.18	39	0.5	0.57	13	0.2
Formal education	0.46	18	0.001	0.90	21	0.75	0.85	64	0.5
Smoke cigarette	2.45	2	0.1	1.59	2	0.6	-	-	-
Smoke hookah	0.87	35	0.4	0.93	24	0.8	0.99	5	0.9
High economic score	0.85	15	0.45	0.6	7	0.34	0.6	20	0.25
Age at marriage 21+	0.66	16	0.1	0.83	8	0.7	0.75	22	0.3
Married for 30+ years	3.52	19	0.001	3.59	19	0.001	1.41	11	0.38

[a]survey in 1997
[b]crude odds ratio for any cervicitis as opposed to non
[c]prevalence(%) of factor in the survey population
[d]significance

The results for reproductive variables on risk of bacterial vaginosis are given in table 4.18. In the Qashgha'i tribe, significant increases in risk were observed for high parity, in terms of numbers of either pregnancies (p <0.004) or deliveries (p <0.001), postmenopausal status (p=0.001), and traditional midwife or neighbour as birth assistant (p <0.001). Significant decreases in risk were observed for birth in maternity hospital (p<0.006), use of contraceptive pill before (p <0.02) or during (p=0.009) the study and also use of any contraceptive (p <0.001). There is a suggestive increase in risk for history of abortion (p=0.09). In the Lor population, significant increases in risk were observed for postmenopausal status (p=0.02), lower risk for use of any contraception(p=0.05) and a suggestive increase in risk for history of abortion(p=0.09).For women in the urban population, there is a significant increasing risk for intercourse in menses (p =0.05) and a significant decrease risk with birth in hospital (9 =0.01).

4.18: Univariate odds ratios effect of reproductive variables on risk of bacterial vaginosis in each survey population

Variables	Population								
	Qashgha'i[a]			Lor			Urban		
	OR[b]	P(%)[c]	P[d]	OR	P(%)	P	OR	P(%)	P
Age at first pregnancy 21+	1.05	26	0.7	1.25	17	0.5	0.85	25	0.6
4 or more pregnancy	1.72	76	0.004	1.13	75	0.6	1.08	48	0.7
History of abortion	1.36	21	0.09	1.76	18	0.09	0.78	25	0.45
4 or more delivery	1.72	73	0.001	1.03	74	0.9	1.38	40	0.26
Postmenopausal	5.54	17	0.001	4.99	5	0.02	-	-	-
Polygamy	0.83	9	0.5	0.94	8	0.9	1.02	2	0.97
Intercourse 3+ time/week	0.82	20	0.3	0.85	26	0.6	1.35	34	0.3
Intercourse in menses	1.21	28	0.2	1.01	25	0.9	1.83	28	0.05
Pill (before)	0.7	32	0.02	0.97	52	0.90.	1.41	38	0.23
Pill (now)	0.62	23	0.009	0.72	20	32	1.02	12	0.9
Contraception (any-now)	0.47	52	0.001	0.47	596	0.05	0.65	81	0.22
Birth in hospital	0.79	10	0.36	1.46	12	0.34	0.44	72	0.01
Birth in maternity hospital	0.69	40	0.01	1.14	37	0.6	1.51	26	0.1
BA neighbor	2.02	77	0.001	0.95	83	0.88	-	-	-

[a]survey in 1997
[b]crude odds ratio for any cervicitis as opposed to non
[c]prevalence(%) of factor in the survey population
[d]significance

Table 4.19 shows backward stepwise regression for predictors of bacterial vaginosis. Increased risk with postmenopausal status ($p<0.001$) and traditional midwife or neighbour as birth assistant ($p=0.02$), and a decreased risk with use of any contraceptive ($p=0.02$) were the significant predictors in the Qashgha'i tribe. In the Lor tribe an increased risk with having been married for more than 30 years($p=0.002$) was the only significant predictor. The risk of bacterial vaginosis in the urban population was decreased for birth in hospital ($p=0.01$).

Table 4.19: Backward stepwise regression results for predictors of bacterial vaginosis in each survey population

Sample	RF[a]	Category	Bacterial vaginosis		OR[b]	95% CI
			NO	Yes		
Qashgha'i	Postmenopausal	No	327(56)	259(44)	1.00	-
		Yes	23(19)	101(81)	4.10	2.44 – 6.88
	Contraceptive (any)	No	133(39)	204(61)	1.00	-
		Yes	214(58)	156(42)	0.69	0.49 – 0.95
	Birth assistant[c]	No	101(63)	60(37)	1.00	-
		Yes	249(45)	300(55)	1.56	1.07 –2.27
Lor	Married for 30^{+} years	No	118(56)	85(43)	1.00	-
		Yes	12(27)	33(73)	3.59	1.75 – 7.36
Urban	Birth in hospital	No	27(47)	31(53)	1.00	-
		Yes	99(66)	51(34)	0.44	0.24 – 0.82

[a]Risk Factor
[b]odds ratio
[c]traditional midwife or neighbour

4.3.3 Reproductive Morbidity Results

Due to the uncertainty of interpretation of the large number of potential significance tests, we did not evaluate risk factors for each reproductive morbidity variable separately, other than comparing their prevalence among the three survey populations. Results are shown in table 4.20. Significant differences were observed for all reproductive morbidity variables except stress incontinence and dysparunia. This is mostly manifested as higher prevalence in the nomadic populations, with the notable exception of clinical signs of erosion and cervicitis

Table 4.20: Frequency and proportion of reproductive morbidity variables in the survey populations

Variables		Population						X^2	df	p
		Qashgha'I		Lor		Urban				
		No	(%)	No	(%)	No	(%)			
Cystocel	Yes	539	65	193	74	127	33			
	No	289	34	69	26	259	67	143	2	0.001
Rectocel	Yes	539	65	170	65	123	32			
	No	290	35	92	35	264	68	128	2	0.001
Stress incontinence	Yes	368	40	129	49	154	40			
	No	461	60	137	51	232	60	5	2	0.08
Cervicitis	Yes	318	38	122	26	133	34			
	No	510	62	140	54	253	66	10	2	0.008
Erosion	Yes	164	20	52	20	144	37			
	No	664	80	209	80	242	63	47	2	0.001
Uterine prolapse	Yes	508	61	138	53	47	12			
	No	321	39	124	47	338	88	258	2	0.001
Dyspareunia	Yes	417	50	131	50	176	46			
	No	412	50	133	50	210	54	2	2	0.3
Candida	Yes	103	12	14	5	25	6			
	No	726	88	245	95	361	94	17	2	0.001
Trichomonas	Yes	102	12	18	7	16	4			
	No	726	88	244	93	370	96	23	2	0.001
Examined by	Yes	408	49	131	49	378	98			
OB-GYN[a]	No	425	51	137	51	7	2	292	2	0.001

[a]obstetricians and gynaecologist

This last is difficult to understand in the light of the cytological findings . We therefore investigated the performance of clinical diagnosis (observation) in comparison with cytology as a gold standard.

Table 4.21 and table 4.22 compares clinical observation of cervicitis and erosion with the diagnoses of cervicitis from the Pap smear test. Sensitivity for cervicitis in Qashgha'i, Lor and Urban populations is poor (41, 52, 40 percent respectively). For Erosion, sensitivity is low in Qashgha'i and Lor populations, but for the urban population it is slightly higher. Both specificity and positive predictive value are relatively high for cervicitis and erosion in all three populations. Percentage of agreement for both cervicitis and erosion is consistent at around 50 % except for erosion in Qashgha'i. The Kappa statistics include poor agreement except for cervicitis in the urban population.

Table 4,21: Comparison of clinical observation with cervicitis diagnosed by PAP test, and evaluation of clinical observation in the survey populations

Population	Clinical Observation		Cervicitis diagnosed by Pap smear	
			Yes	No
Qashgha'i	Cervicitis	Yes	295	23
		No	429	73
	Erosion	Yes	157	9
		No	570	87
Lor	Cervicitis	Yes	111	10
		No	101	35
	Erosion	Yes	48	4
		No	163	41
Urban	Cervicitis	Yes	89	23
		No	134	68
	Erosion	Yes	95	22
		No	128	69

Table 4.22: Evaluation of clinical observation in the survey population

Population	Clinical Observation	Evaluation					
		Sensitivity	Specificity	PV^{+a}	PV^{-b}	Agreement	Kappa(%)
Qashgha'i	Cervicitis	41	76	93	15	45	7
	Erosion	21	91	95	13	36	16
Lor	Cervicitis	52	78	92	26	57	15
	Erosion	23	91	52	20	44	30
Urban	Cervicitis	40	75	79	34	50	48
	Erosion	43	75	81	35	52	15

[a]predictive value positive
[b]predictive value negative

4.3.4 Relation of Bacterial Vaginosis and Reproductive morbidity to cervicitis

Table 4.23 shows the effect of bacterial vaginosis on risk of any cervicitis and severe cervicitis adjusted only for survey population and adjusted for survey population, age, oral contraception now and previously , other contraception, postpartum bleeding and number of pregnancies (the significant risk factors plus survey population). There was a significant increased risk (of the order of 50%) of any cervicitis associated with bacterial vaginosis. There was a significant 4-5-fold increase in risk of severe cervicitis associated with bacterial vaginosis.

Attributable fraction calculations suggest that bacterial vaginosis accounts for around 20% of total cervicitis and around 60% of severe cervicitis cases.

Table 4.23: Effect of bacterial vaginosis on risk of any cervicitis and severe cervicitis adjusted only for survey population and adjusted for survey population, age, oral contraception now and previously, other contraception, postpartum bleeding and number of pregnancies

Outcome	Adjusted	OR	95% CI	Attributable risk(%)
Any cervicitis	Population only	1.50	1.06-2.11	19
	Multiple adjustment	1.64	1.42-3.69	24
Severe cervicitis	Population only	5.02	2.41-10.46	66
	Multiple adjustment	4.15	1.96-8.78	60

Table 4.24 shows the results of a univariate analysis of reproductive morbidity variables with risk of cervicitis. In all three populations, clinical observation of cervicitis or erosion is significantly associated with cervicitis. As one would expect there is a negative reduction in risk of cervicitis with postpartum bleeding in the Qashgha'i (p =0.05).

Table 4.24: Univariate odds ratios-effect of reproductive morbidity variables and clinical observations on risk of cervicitis in the survey populations

Variables	Population								
	Qashgha'i[a]			Lor			Urban		
	OR[b]	P(%)[c]	P[d]	OR	P(%)	P	OR	P(%)	P
Cystocel	1.28	66	0.2	2.34	74	0.01	0.93	34	0.7
Rectocel	1.41	66	0.1	1.69	66	0.1	1.01	33	0.9
Stress incontinence	1.13	44	0.5	1.20	48	0.5	0.82	39	0.4
Ceervical erosion	2.61	20	0.006	3.01	20	0.03	2.32	37	0.002
Cervicitis (observation)	1.18	39	0.002	3.84	47	0.001	1.96	30	0.01
Uterine prolapse	1.23	61	0.3	1.70	53	0.1	1.49	11	0.3
Dyspareunia	0.84	50	0.4	0.75	50	0.3	0.82	45	0.4
Candida (observation)	1.10	13	0.7	2.87	5	0.2	1.02	7	0.9
Trichomonas (observation)	1.42	12	0.3	3.83	7	0.1	1.23	4	0.7
Dyspareunia	0.84	50	0.4	0.75	50	0.3	0.82	45	0.4
Postpartum Fever	1.14	7	0.7	1.04	7	0.9	-	0.3	-
Postpartum infection	0.92	7	0.8	2.56	10	0.1	-	0.3	-
Postpartum bleeding	0.51	7	0.05	1.14	20	0.7	-	0.3	-
Examined (by OB-GYN)	1.10	49	0.6	0.85	50	0.6	-	98	-

[a]survey in 1997
[b]crude odds ratio for any cervicitis as opposed to non
[c]prevalence(%) of factor in the survey population
[d]significance

4.5 Discussion

In this study, we found a significant increase in risk of cervicitis in association with contraceptive use in the non-nomadic urban population and the partly settled Lor population. In the Qashqua'i population, although there were univariate effects of contraception, these were not significant when adjusted for age and postpartum bleeding. It may be that in the former two populations, the inflammatory changes are more related to infections transmitted in coitus, whereas in the latter they are associated with infections contracted during childbirth. This is possible, as in the Qashqua'i birth usually takes place in a tent with no professional medical support. The association with contraception use is consistent with previous results in the USA (*11*). In an Indian population with similar cervicitis rates to the Qashqua'i, there was an association of high parity with cervicitis (*12*), again consistent with infectious agents being transmitted in childbirth. Association with parity and the reduced risk in postmenopausal women are consistent with this.

Analysis of effects on risk of bacterial vaginosis gave similar results to those for cervicitis but suggested both sexual transmission of infection and birth practice in the aetiology of bacterial vaginosis in all three population (*11,13*). The sexually transmitted element is consistent with the literature, in which bacterial vaginosis has been observed to be correlated with sexually transmitted agents such as HPV and chlamydia in both developed (*13*) and developing countries (*12*).We found a negative association of bacterial vaginosis with hospital birth in the urban women and positive association of using a neighbour or traditional midwife as birth assistant in nomadic Qashqua'i women. The association of bacterial vaginosis with childbirth does not seen to be well researched elsewhere.

Finally we found a very strong positive association between bacterial vaginosis and cervicitis. Bacterial vaginosis was a powerful risk factor for cervicitis even after adjustment for other risk factors for cervicitis (Table 4.23). Attributable risks were also high, suggesting that bacterial vaginosis may be implicated in up to 60% of severe cervicitis cases. Other studies have found similar results with respect to presence of cervicitis in population from India (*12*) and the USA (*11*). Bacterial vaginosis has also been associated with measured risk of pelvic inflammatory disease (*14,15*). To our knowledge, ours is the first study demonstrating and enhanced correlation of bacterial vaginosis with severe cervicitis.

Clearly, there are other agents which need to be taken into account in order to reliably quantify the role of bacterial vaginosis in cervicitis, notably HPV and Chlamydia trachomatis, both of which have been implicated in the aetiology of inflammatory atypia in the past (*11,12*). Facilities for testing for these agents are not available locally, and we examine some surrogates in later chapters. In conclusion, we have found some evidence of a role of infections contributed to childbirth in the aetiology of both bacterial vaginosis and cervicitis. We have also found evidence that bacterial vaginosis itself involved in the aetiology of cervicitis, particularly severe cervicitis.

The attributable risk calculations suggest that around 20% of all cervicitis cases and around 60 % of severe cervicitis cases may be attributable to bacterial vaginosis. It is interesting to ascertain whether variation between the three populations in bacterial vaginosis rates explain a similar proportion of the variation in cervicitis rates. The adjusted estimate of relative risk of cervicitis associated with bacterial vaginosis was 1.64. In the Qashgha'i , lor and urban women surveys, the populations with bacterial vaginosis were 51% , 49% and 40% respectively.

If P is the probability of having cervicitis in women without bacterial vaginosis, then the expected populations with cervicitis, based on bacterial vaginosis status are in table 4.25.

Table 4.25:Expected proportions with cervicitis based on Bacterial Vaginosis status

Qashgha'i	P H 0.49 + 1.64P H 0.51 = 1.33P
Lor	P H 0.51 + 1.64P H 0.49 = 1.31P
Urban	P H 0.60 + 1.64P H 0.40 = 1.26P

This gives expected relative proportions with cervicitis as 1.04 and 1.05 for the lor and Qashgha'i respectively relative to urban women. The observed relative proportions (table 4.6) were 1.20 and 1.24. Thus of the 24% excess risk in the Qashgha'i tribe 5/24 = 21% of the excess risk in the Qashgha'i is explained by bacterial vaginosis. The variation in bacterial vaginosis explains a proportion of the differences between populations with respect to cervicitis, which is consistent with the 24% attributable risk (table 4.23).

Similar calculations for severe cervicitis suggest that bacterial vaginosis explains 100% of the excess in the Qashgha'i. The 60% figure for attributable risk lies approximately midway between these estimates.

In both cases, the estimates above are tentative and informal. It is, however, interesting to note that the attributable risk figures approximately agree with proportions of the differences between populations, which can be explained by bacterial vaginosis.

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Chapter 5

Association of cervicitis with surrogates for chlamydia and human papillomavirus

5.1 Laboratory Facility

During the study period, there was no facility in Iran, for testing to detect HPV and chlamydial infections directly. For this reason we used surrogate observations from the Pap smears that were collected from the survey population. This is clearly unsatisfactory but may be inevitable in developing countries and populations resident in remote locations.

5.2 Koilocytosis and Metaplasia as surrogates for HPV

Ideally, human papillomavirus (HPV) infection should be confirmed by DNA methods such as polymerase chain reaction or hybrid capture (*1-4*). In the absence of these methods, we seek surrogates observable on the Pap smear. One such is kiolocytosis, first described by Koss in 1956 (*5*).

Inflammatory changes and cellular atypia associated with HPV infection or even mildly dysplastic changes are sometimes reported in the atypia-less-than-dysplasia category. The clinical significance of such observation is not clear(*6*). The diagnosis of HPV infection before the availability of DNA methods focused on the identification of Koilocytotic cells, which occur in the outer layer of squamous cells scraped from the cervix. The Koilocytotic cell is considered highly diagnostic for HPV infection, and is the single most important cytologic feature attributable to such infection (*7-9*). However, the absence of Koilocytes does not always exclude a productive HPV infection.

The presence of Koilocytes in a smear, in the absence of dysplastic cells, can be misleading. Koilocytes occur in productive HPV infections in which the terminal differentiation of squamous epithelial cells within a lesion is sufficient to produce them. However, undifferentiated CIN 3 lesions or invasive cancers may have adjacent areas of lower grade lesions that support Koilocytosis (*10*). Other factors may also be influencial. For example in one study the presence of HPV changes (koilocytosis and condyloma) around the neoplastic epithelium correlated with a mean age group younger than that of those without HPV changes.(*11*).

Efforts to prevent cervical cancer have successfully focused on the identification and elimination of cervical intraepithelial neoplasia (CIN), which, in turn, has relied on the efficacy of Pap smear screening. Because of the close relationship between HPV and cervical cancer, it may be possible to refine such screening by including signs of HPV infection among the precancerous lesions, as evidenced by the recent Bethesda classification recommendations (*12*), where HPV-related lesions and mild CIN are believed to have a similar precancerous potential (*13*).

The use of Koilocytes as a marker for HPV infections is thus supported by the research results. However, the identification of Koilocytes is a subjective exercise, and strict criteria are necessary to obtain this good correlation but diagnosis is possible based on the cytological findings in the smear (*13*). Cytology of exfoliated cells is noninvasive and fairly inexpensive. The most common characteristic cytologic finding of HPV infection is Koilocytosis; dyskaryosis, atypical basal cells, metaplasia, and multinucleation have also been described. Cytology has good specificity, but only fair sensitivity. Histologic findings in genital warts include basal cell hyperplasia, acanthosis, papillomatosis, koilocytosis, parakeratosis, and mild

nuclear atypia. The Koilocyte is the most specific histologic marker for HPV infection, except for HPV types 16 and 18 (*14*).

Metaplasia of the cervix is a variant of low-grade squamous intraepithelial lesions. It is frequently associated with human papilomavirus (*15*). In general, when a cytologic diagnosis of metaplastic cells is made on a Papanicolaou smear, the histologic correlate will be a squamous intraepithelial lesion, or benign reactive process (*16,17*). Because of the multiple possible sources of metaplasia, it is a very non-specific sign.

5.3 Histiocytes as a surrogate for Chlamydia infection

Barnes has reviewed the subject of non-culture-based diagnostic tests for chlamydial infections extensively (*18*). The literature contains reports suggesting that the Papanicolaou smear is a useful way of diagnosing chlamydial infection in women in the absence of DNA or immunofluoresence tests (*19*). Detailed evaluations of the character of the inflammatory cell response in endocervical smears are predictive of chlamydial infection, but these studies are not routinely performed by most cytology laboratories (*20*)

One would clearly expect chlamydia trachomatis (CT) to be correlated with inflammatory changes. It is of some interest to quantify this in a population with a high prevalence of such inflammatory change.

The presence of polymorphonuclear (PMN) cells on gram stains (five polymorphonuclear cells high-powered field) has been observed to be strongly associated with chlamydial infection (*21*).

The "gold standard" for diagnosis of CT cervical infections was considered in the past to be cell culture in treated McCoy cells. However, cell culture is expensive, requires skilled technical support and requires proper transport to ensure that viable material is present to culture CT infection. Because of this, cell culture is generally offered only in reference laboratories, with test results available only after several days. More recently, other tests have become available that have eliminated much of the expense of and difficulty in detecting CT infection (*22*).

The concept of detecting CT in cervical Papanicolaou smears was first advanced by Naib and. Kiviat (*20,23*). Kiviat et al(*20*) used multivariate analysis to determine the best morphologic indicators for the diagnosis of CT infection in cervical smears taken from women at a sexually transmitted disease clinic. In a population of 265 women, CT infection was found to be associated with increased numbers of transformed lymphocytes, polymorphonuclear neutrophils and histiocytes and also reactive or atypical metaplastic cells, the presence of >30 histiocytes in at least three high-power fields and / or the presence of transformed lymphocytes was associated with CT infection. The importance of identifying CT infection among high-risk groups has been well documented (*21*).

In our study, we had the data to use the criteria of Kiviat et al(*20*). For purposes of evaluating the association with cervicitis, however, we did not do so as this would have involved using PMNL's as diagnostic factors for both CT and cervicitis, thus introducing an artificial structural correlation between the two.

5.4 Methods and Strategy

Our original cytologist noted the presence of metaplasia, and the presence of large numbers of histiocytes, but did not specifically attempt to identify koilocytosis. Consequently, we arranged to have 88 smears read for koilocytosis, blind to original findings, by an independent cytologist (Dr Alistair Williams of the University of Edinburgh).

Our aim was to use the presence of histiocytes in large numbers as an indicator of CT infection, and the presence of koilocytosis and/or metaplasia as an indicator of HPV infection. We then established the associations between these indirect indicators and the presence or absence of cervicitis.

It is not clear how effective are koilocytosis and metaplasia as indicators of HPV infection. For CT, however, Lindner et al (*24*) found that large numbers of histiocytes had a sensitivity of 74% and specificity of 46%.Kiviat et al (*20*) found that large numbers of histiocytes and/or large numbers of transformed lymphocytes had a sensitivity of 95% and specificity of 75%.

5.5 Results

Table 5.1 shows the association between metaplasia and cervicitis. Clearly it is strongly and significantly positively related to both presence and severity of cervicitis ($p<0.001$). Attributable risks of around 40% were observed for both any cervicitis and severe cervicitis. Among the 88 slides reviewed for koilocytosis, no cases were observed at all. This suggests that the metaplasia observed may be indicative of processes other than HPV.

The association of increased numbers of histiocytes with cervicitis is shown in Table 5.2. There is a very strong and significant association with presence of any cervicitis ($p<0.001$), but a weaker, non-significant association with severe cervicitis. The attributable risk for any cervicitis was 86%. The multivariate adjusted results show considerably attenuated relationships with cervicitis. The proportion of all cervicitis cases estimated to be attributable to histiocytes as an indicator of CT infection was 47% after multivariate adjustment.

Table 5.1 Effect of metaplasia on risk of any cervicitis and severe cervicitis

Cervicitis	Metaplasia		OR	95% CI	Attributable risk %
	Yes No (%)	No No (%)			
None	13(5)	223(20)	1.00	-	-
Any	273(95)	887(80)	5.27	2.97 – 9.39	46
Total	286(20)	1110(80)			
Moderate or better	256(90)	1078(97)	1.00	-	-
Severe	30(10)	32(3)	3.94	2.35 – 6.61	37
Total	286(20)	1110(80)			

Prevalence=20%

Table5.2 Effect of histiocytes on risk of any cervicitis and severe cervicitis

Cervicitis	Histiocytes		OR	95% CI	Attributable risk%
	Yes No (%)	No No (%)			
None	90(9)	125(45)	1.00	-	-
Any	938(91)	150(55)	8.69	6.29 – 11.97	86
Total	1028(79)	275(21)			
Moderate or better	974(95)	267(97)	1.00	-	-
Severe	54(5)	8(3)	1.85	0.87-3.94	40
Total	1028(79)	275(21)			

Table 5.3 Effect of histiocytes on risk of any cervicitis and severe cervicitis adjusted for survey population, , age , number of pregnancies , postpartum bleeding, use of oral contraceptives at the time of survey, and use of oral contraceptives in past

Outcome	OR	95% CI	Attributable risk %
No cervicitis	1.00	-	-
Any cervicitis	2.12	1.70 – 2.47	47
Moderate or better	1.00	-	-
Severe cervicitis	1.75	0.73-4.22	37

5.6 Discussion and implications of use of indirect indications

Lindner et al (*24*) found that the sensitivity of large numbers of histiocytes as an indicator of CT infection was 74%, and its specificity was 46%. Clearly our observed prevalence of histiocytes of 79% is not compatible with these figures. Thus it is likely that either our sensitivity is better or our specificity poorer. Kiviat et al (*20*) found that increased numbers of histiocytes and/or the presence of transformed lymphocytes had a sensitivity of 95% and specificity of 75%. If we assume, therefore, that the sensitivity and specificity of increased number of histiocytes as an indicator of CT lie midway between Lindner et al (*24,25*)and Kiviat et al's (*20*) estimates, we have a sensitivity of 84% and specificity of 60%. This therefore, with the observed prevalence of 79% gives us a formula for the true prevalence p,

$$0.79 = 0.84\,p + 0.40\,(1\text{-}p)$$

i.e. the true prevalence is 89% . There is considerable uncertainly around this figure but a likely interpretation is that the true prevalence at least exceeds the 50% in Lindner et al's (*24*)study.

With a sensitivity of 84%, specificity of 60% and prevalence of 89%, the positive predictive value is estimated as 95% and the negative predictive value as 31%.

We can use the sensitivity of 0.84 and specificity of 0.60 within categories of cervicitis to impute the proportions with and without CT infection by cervicitis state and therefore the estimated odds ratios associated with CT itself rather than histiocytes. In those with no cervicitis, 90 (42%) had an increased number of histiocytes and 125 did not. The estimated proportion with CT infection is calculated using

$$0.42 = 0.84p + 0.40(1 - p)$$

Where p is the proportion with CT infection. This gives p=0.05, and a total number of 11 with CT. Applying the same method to those with cervicitis, we estimate that all 1088 are positive for CT infection. If we assume that at least one of these subjects is negative we have table 5.4.

Table 5.4 Imputed CT infection by cervicitis status

Cervicitis	Estimated CT infection	
	No	Yes
None	204	11
Any	1	1087

This gives an OR of 20, considerably more than the 8.81 for histiocytes. It is consistent with the convention that misclassification dilutes effects on risk, but it should be noted that there is considerable uncertainty around our estimate of 20.The same procedure applied to severe cervicitis gives Table 5.5

Table 5.5 Imputed CT infection by severe cervicitis/moderate or better

Cervicitis status	Estimated CT infection	
	No	Yes
Moderate or better	174	1067
Severe	1	61

This gives an odds ratio of 10, again considerably greater than that of 1.85 observed for histiocytes alone. Again, it should be borne in mind that there is a great deal of uncertainty on the OR of 10.

We do not have reliable data on the sensitivity, specificity and predictive values for metaplasia as a surrogate for HPV. We do know that it is a very approximate indication, that metaplasia itself in Table 5.1 shows a weaker relationship with cervicitis than does presence of large numbers of histiocytes and that no cases of Koilocytosis were observed in the 88 slides revised.

The tentative conclusion from the above is therefore that Chlamydia trachomatis infection is more likely to account for a larger population of the cervicitis cases than HPV infection.

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Chapter 6

Repeatability, persistence and reproducibility of cervicitis scores. Effects of imperfect measurement on risk associations observed

6.1 Measurement error

In the judgment of severity of inflammation from cytological smears there is clearly room for errors of classification (*1-4*). In general in epidemiology (with some exceptions), the effect of misclassification of risk factors is to dilute observed estimates of effect on risk (*5-7*). It can be seen intuitively that misclassification of the disease endpoint will usually have the same effect (including some positives among the negatives and vice versa is liable to attenuate differences between the two groups). In this chapter we estimate the likely extent of such misclassification and its implications for the association of various factors with risk of cervicitis.

6.2 Repeatability/persistence of cervicitis

Table 6.1 shows the cervicitis scores at both surveys five years apart (1991-2 and 1996-7) for those 811 women who were included in both. Only 226 (28%) had exactly the same cervicitis score on both occasions. Of the 585 whose score changed, 272 (46%) had a more severe score at the second survey and 313 (54%) had a less severe score. The considerable differences at individual level between first and second score are arguably too large to be due to classification errors alone and must therefore at least partly be due to transience of the cervicitis states.

Table 6.2 shows the cervicitis score dichotomized to no cervicitis/any cervicitis. Here the percentage agreement between the two occasions is of course higher, at 71% (577 out of

811). Of those who had any cervicitis noted at first survey, the vast majority still had some at the second. For those with no cervicitis at first survey, 94% had cervicitis noted at the second. This high incidence is consistent with the high prevalence. The two tables together suggest a degree of misclassification generally, a high incidence of cervicitis and considerable transience or misclassification of the individual categories of cervicitis. This can be seen from Table 6.3, where of those with severe cervicitis at first survey, 95% had a score less than severe at the second.

The next section, reporting on independent rereading of slides by a different cytologist, should throw light on the proportion of observed changes which are due to misclassification and which to real changes in cervicitis status.

Table 6.1 Cervicitis scores at first and second survey in 811 Qashgha'i women

Second survey- cervicitis	First survey- cervicitis			
	None No (%)	Mild No (%)	Moderate No (%)	Severe No (%)
None	10 (6)	17 (9)	45 (15)	24 (15)
Mild	47 (30)	62 (32)	96 (32)	43 (26)
Moderate	89 (56)	98 (52)	146 (49)	88 (54)
Severe	12 (8)	13 (7)	13 (4)	8(5)

Table 6.2 Cervicitis (none/any) at first and second surveys

Second survey cervicitis	First survey- cervicitis	
	None No (%)	Any No (%)
None	10 (6)	86 (13)
Any	148 (94)	567 (87)

Table 6.3 Severe cervicitis at first and second surveys

Second survey- cervicitis	First survey- cervicitis	
	Moderate or better No (%)	Severe No (%)
Moderate or better	610 (94)	155 (95)
Severe	38 (6)	8(5)

6.3 Reproducibility of cervicitis classification

From the second survey, we selected a stratified random sample of 72 Qashgha'i subjects (16 no cervicitis, 14 mild, 29 moderate and 13 severe), and had the cervical smears re-read for cervicitis by an independent cytologist/pathologist (Dr Alistair Williams, University of Edinburgh). Table 6.4 shows the results cross-classified with the original Iranian cytologist's findings. The level of agreement is 42% (30 out of 72), with a kappa of 0.22 (95% CI 0.07-0.37). Table 6.5 shows the results with cervicitis dichotomized to severe or not. Again, as one would expect, agreement is better, at 85%, and a kappa of 0.29 (95% CI 0.007-0.58).

Table 6.6 shows the corresponding results for any cervicitis compared to none, with 83% agreement and a kappa of 0.49 (95% CI 0.25-0.73).

Duffy et al (*5*) show that in such a 2 by 2 classification, the probability of correct classification is estimated as

$$\alpha = 0.5 + 0.5 \times \sqrt{\frac{N - 2(c+d)}{N}}$$

where N is the total number classified twice (in this case 72- see Table 6.6) and c and d are the numbers of disagreements (in this case 6 and 6). This gives a probability of correct classification of whether or not cervicitis is present, regardless of severity, of 0.91, i.e. 9%

misclassification. Similar calculations for Table 6.5 give an estimate of 8% misclassification of severe cervicitis/moderate or better.

Table 6.4 Iranian cytologist's findings by Edinburgh cytologist's findings

Edinburgh cytologist-cervicitis	Iran cytologist- cervicitis			
	None No (%)	Mild No (%)	Moderate No (%)	Severe No (%)
None	10 (63)	3 (19)	2 (13)	1 (6)
Mild	5 (14)	9 (26)	19 (54)	2 (6)
Moderate	0 (0)	2 (12)	8 (47)	7 (41)
Severe	1 (25)	0 (0)	0 (0)	3 (75)

Table 6.5 Severe cervicitis- Iranian cytologist's findings by Edinburgh cytologist's findings

Edinburgh cytologist-cervicitis	Iran cytologist- cervicitis	
	Moderate or better No (%)	Severe No (%)
Moderate or better	58 (98)	10 (77)
Severe	1 (2)	3 (23)

Table 6.6 Any cervicitis compared to none- Iranian cytologist's findings by Edinburgh cytologist's findings

Edinburgh cytologist-cervicitis	Iran cytologist- cervicitis	
	None No (%)	Any No (%)
None	10 (63)	6 (11)
Any	6 (37)	50 (89)

It should be noted that for any cervicitis compared with none, the disagreement between the two values is roughly symmetric, suggesting (although, not definitely establishing) that misclassification is equally likely in either direction. The same cannot be assumed for severity of cervicitis, where the Iranian cytologist tended to classify greater severity. The results indicate generally good agreement between cytologists and suggest relatively low rates of misclassification. Thus, differences between individuals' cervicitis states several years apart are mostly likely to be due to real changes in cervicitis over time. This is probably due to clearance of former infections and contraction of new infections

6.3.1 Correction of risk estimates for misclassification of cervicitis

An approximate correction for the bias caused by misclassification of the endpoint is to divide the logarithm of the observed odds ratio by (2α-1), where α is the probability of correct classification(*8*). This means raising the odds ratio to the power of x, where

$$x = \frac{1}{2\alpha - 1}$$

Take the example of history of giving birth in a maternity hospital in Chapter 3 (Table 3.6) as a risk factor for cervicitis. We have α=0.91, therefore x=1.22 and an uncorrected multivariate adjusted odds ratio of 1.30. The corrected odds ratio is therefore $1.30^{1.22}$ =1.38. If we consider the effect of bacterial vaginosis in chapter 4 (Table 4.23), the uncorrected multivariate adjusted odds ratio is 1.64. Again x=1.22, so the odds ratio corrected for misclassification of cervicitis is $1.64^{1.22} = 1.83$.

Considering now the effect of bacterial vaginosis on risk of severe cervicitis, we have an uncorrected multivariate adjusted odds ratio of 4.15. From Table 6.5 we calculate α=0.92, and therefore x=1.19. The corrected odds ratio is therefore $4.15^{1.19} = 5.44$.
Of course, this assumes symmetry of misclassification, which may be untenable for severe cervicitis

6.4 Conclusions

From the above, we should bear in mind that uncertainty in classification implies that the true effects of various factors on risk of cervicitis are likely to be slightly larger than those observed in chapters 3-5. We estimate informally that the log odds ratios are underestimated by around 20%.

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Chapter 7

Discussion and Implications

7.1 Risk Factors for Cervicitis and bacterial vaginosis

This study confirms high prevalence rates of cervicitis, as defined by inflammation on cervical smear specimens, in nomadic, semi-nomadic and settled urban populations in Southern Iran. There is evidence of some misclassification of cervicitis and arguably a tendency to overestimate its severity, but these are not sufficient to account for the high rates observed. In a series of cross-sectional surveys, we found a number of bacteriological and pathological factors to be associated with cervicitis. In particular, bacterial vaginosis was strongly associated with risk of cervicitis (RR=1.5). In addition, various risk factors for cervicitis, mainly related to childbearing or sexual habits, were identified.

In this study, we found a significant increase in the risk of cervicitis in association with contraceptive usage in the non-nomadic urban (RR= 2.48) population and the semi-nomadic Lur population (RR=2.19). Although there were univariate effects of contraception, in the Qashqua'i population, these were not significant when adjusted for age and postpartum bleeding. This may be because in the former two populations, inflammatory changes are more closely related to infections transmitted in coitus, whereas in the latter they are associated with infections contracted during childbirth. This is feasible, since among the Qashqua'i, birth usually takes place in a tent without professional medical support.

The association with contraception use in non-nomadic women is consistent with previous results in the USA (*1*). In an Indian population with similar cervicitis rates to the

Qashqua'i, there was an association of high parity with cervicitis (*2*), again consistent with infectious agents being transmitted during childbirth in developing populations.

Analysis of effects on risk of bacterial vaginosis produced similar results to those for cervicitis but suggested the importance of both sexual transmission of infection and birth practices in the aetiology of bacterial vaginosis in all these population, again consistent with results in other populations (*1,3*) .

The sexually transmitted element is consistent with the literature, in which bacterial vaginosis has been observed to be correlated with sexually transmitted agents such as HPV and chlamydia in both developed (*4*) and developing countries (*2*).We found a negative association of bacterial vaginosis with hospital birth in the urban women (RR=0.44) and a positive association of using a neighbour or traditional midwife as a birth assistant in nomadic Qashqua'i women (RR=2.02). The association of bacterial vaginosis with childbirth does not seem to be well researched elsewhere.

Finally we found a very strong positive association between bacterial vaginosis and cervicitis. Bacterial vaginosis was a powerful risk factor for cervicitis even after adjustment for other risk factors for cervicitis (RR=1.64).

Attributable risks were also higher, suggesting that bacterial vaginosis may be implicated in 60% of cases of severe cervicitis cases. Other studies have found similar results with respect to presence of cervicitis in populations from India (*2,3*) .Bacterial vaginosis has also been associated with increased risk of pelvic inflammatory disease (*5,6*). To our knowledge, however, this is the first study demonstrating an enhanced correlation of bacterial vaginosis with severe cervicitis.

Clearly, there are other agents which need to be taken into account in order to reliably quantify the role of bacterial vaginosis in cervicitis, notably the HPV and Chlamydia trachomatis, both of which have been implicated in the aetiology of inflammatory atypia in the past (*1,2*).

7.2 Surrogates for Chlamydia and Human Papillomavirus

Due to the absence of definitive testing facilities for chlamydia trachomatis and HPV, we studied surrogates for these which were observable from the cervical smears. We used enhanced numbers of histiocytes as an indirect indicator of chlamydia and the presence of koilocytosis or metaplasia as indirect indicators of HPV infection. Histiocytes and metaplasia were routinely recorded locally for almost all of the cervical smears, as part of the cytology laboratory's routine procedure. Koilocytosis was not available routinely, but a stratified subsample of 88 smears were read for koilocytosis by an external pathologist.

We did not find any Koilocytotic cells from the 88 reviewed slides as a diagnostic feature for HPV, but we found a strong association between metaplasia and both the presence and severity of cervicitis ($p=0.001$) in 1396 cytologic slides. It is not clear how effective metaplasia is as one of the indicators of HPV. The absence of koilocytosis suggests that the metaplasia observed may be indicative of processes other than HPV. The results emphasise the unsatisfactory nature of observation of the smear specimen alone as a diagnostic procedure for HPV.

Culture is the gold standard to diagnose chlamydia. This is a sophisticated technique, which is very expensive, requiring fast transfer to a well equipped laboratory. This is not practicable in a nomadic population and local resources for such testing were not available. Therefore in this study we did not use the culture method. Even though observation of

large numbers of histiocytes on the cervical smear is less precise and less accurate, it is feasible in a nomadic population, and was therefore used as a surrogate for culture to detect chlamydial cervicitis.

In our study, we found a strong positive association between high levels of histiocytes and presence of cervicitis (RR=8.69). Even taking account of the imprecision of this as an indicator of chlamydial infection, the evidence of an association with chlamydia is still strong, which is consistent with the literature (*7,8*).

7.3 Repeatability, persistence and reproducibility of cervicitis scores

In the judgment of severity of inflammation from cytological smears, we should bear in mind that uncertainty in classification may imply that the true effects of various factors on risk of cervicitis are likely to be slightly larger than those observed in chapters 3-5. We estimate informally that the log odds ratios are underestimated by around 20%. It is also possible that some risk factors have gone unobserved as a result of the misclassification.

One should also bear in mind that in addition to random misclassification, the rereading of a subsample of smears suggests that while the external pathologist for the most part agreed with the local findings on the presence of cervicitis, the local classification of severity of cervicitis was consistently higher than that of the external pathologist. This can have two implications: firstly, that severe cervicitis is less common in Southern Iran than the local findings suggest; secondly, that associations with severity of cervicitis may be considerably underestimated as a result of large numbers of mild to moderate cases being included among the severe, and so diluting observed associations with severe cervicitis.

7.4 *Conclusions and recommendations*

In terms of the reproductive health status of the populations studied, there are several basic conclusions. Before listing these, it must be made clear that any morbidity identified in the participants in the study will be treated and appropriate follow-up carried out.

The first conclusion about the populations is that cervical inflammation is widespread in all three: nomadic Qashga'i, semi-nomadic Lur, and settled urban women. Secondly, there is little evidence on the extent of HPV infection, by the absence of koilocytosis in a subsample of smears is at least suggestive that HPV is unlikely to be the major cause of the cervicitis observed or to be a major health problem in the populations under study here. The high rates of cervicitis, with the corresponding high prevalence of enhanced numbers of histiocytes strongly suggest that chlamydial infection may be the chief problem here.

The high levels of bacterial vaginosis and its association with cervicitis also suggest a bacterial aetiology of the latter. The association with parity and birth practices in the Qashga'i suggests that some of the inflammation may be due to infections contracted in childbirth, although this does not rule out sexually transmitted factors.

One might be tempted to conclude from the low rates of dyskariosis in the Qashga'i women that Pap smear screening is not worthwhile in this population. This would probably be the wrong interpretation. In the first survey, there were only two cases of dyskariosis, but both transpired to be cervical carcinoma in situ on diagnostic workup. Finally, the inflammation itself may be impeding the diagnosis of dyskariosis on the smears. If future public health activity reduces the rates of infection with the agents causing the inflammation, more cases of dyskariosis, which were previously occult, may be found.

The following recommendations, in terms of public health interventions follow from the work reported here:

1. Efforts should be made to identify the infectious agent or agents responsible for the high prevalence of cervicitis, as defined by inflammation on the Pap smear, in all populations in this area of Southern Iran. Since one strongly suspected agent is chlamydia trachomatis, this should involve surveys to determine the prevalence of culture-confirmed chlamydial infection in the nomadic, non-nomadic and semi-nomadic populations, and its correlation with cervicitis.
2. If chlamydial infection is identified as having a high prevalence resources should be directed to prevention and treatment. If not, or if the presence of chlamydia is high but does not seem to be responsible for the high rates of cervicitis, the search for infectious agents and practices likely to lead to infection should continue. Other possible candidates are chronic bacterial, microbial or fungal infections. A viral cause such as herpes simplex is also a possibility.
3. Treatment of infections should also take place for spouses. This has been successful in the past in these populations in treatment of trichomoniasis identified in the female partner.
4. There is clearly a need for better maternity support for the nomadic women.
5. For the moment, efforts should continue to improve reproductive health in the nomadic women; in particular, cervical smear screening should continue in so far as this is possible.

Research issues which should be followed up include:

1. As stated above, potential sources of the high rates of inflammation should be investigated. This is a research as well as a public health issue.
2. Further research should be carried out within the context of the screening programme. As better hygiene and delivery of reproductive and maternal health

develops, one would expect the inflammation rates to decline. Follow-up research should take place to confirm whether this happens, and to observe any corresponding changes in rates of dyskariosis on smears.

3. Our findings are suggestive that HPV infection is not a major problem in these populations, but this is by no means a firm conclusion. Surveys should take place in these populations to determine the true prevalence of DNA-confirmed HPV infection. With the local resources, these surveys will have to be small, but small surveys would nevertheless be valuable.
4. Studies of male reproductive health and sexual practices would be valuable, but this is difficult in the context of the local culture.

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